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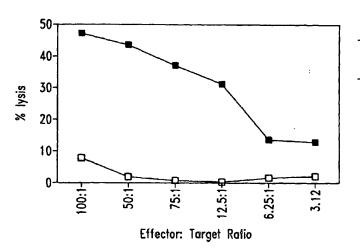
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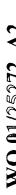
(54) Title: COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER



p502S transduced fibroblasts

--- control fibroblasts

(57) Abstract: Compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer, are disclosed. Compositions may comprise one or more prostate tumor proteins, immunogenic portions thereof, or polynucleotides that encode such portions. Alternatively, a therapeutic composition may comprise an antigen presenting cell that expresses a prostate tumor protein, or a T cell that is specific for cells expressing such a protein. Such compositions may be used, for example, for the prevention and treatment of diseases such as prostate cancer. Diagnostic methods based on detecting a prostate tumor protein, or mRNA encoding such a protein, in a sample are also provided.



# COMPOSITIONS AND METHODS FOR THERAPY AND DIAGNOSIS OF PROSTATE CANCER

#### **TECHNICAL FIELD**

The present invention relates generally to therapy and diagnosis of cancer, such as prostate cancer. The invention is more specifically related to polypeptides comprising at least a portion of a prostate tumor protein, and to polynucleotides encoding such polypeptides. Such polypeptides and polynucleotides may be used in vaccines and pharmaceutical compositions for prevention and treatment of prostate cancer, and for the diagnosis and monitoring of such cancers.

#### BACKGROUND OF THE INVENTION

Prostate cancer is the most common form of cancer among males, with an estimated incidence of 30% in men over the age of 50. Overwhelming clinical evidence shows that human prostate cancer has the propensity to metastasize to bone, and the disease appears to progress inevitably from androgen dependent to androgen refractory status, leading to increased patient mortality. This prevalent disease is currently the second leading cause of cancer death among men in the U.S.

In spite of considerable research into therapies for the disease, prostate cancer remains difficult to treat. Commonly, treatment is based on surgery and/or radiation therapy, but these methods are ineffective in a significant percentage of cases. Two previously identified prostate specific proteins - prostate specific antigen (PSA) and prostatic acid phosphatase (PAP) - have limited therapeutic and diagnostic potential. For example, PSA levels do not always correlate well with the presence of prostate cancer, being positive in a percentage of non-prostate cancer cases, including benign prostatic hyperplasia (BPH). Furthermore, PSA measurements correlate with prostate volume, and do not indicate the level of metastasis.

In spite of considerable research into therapies for these and other cancers, prostate cancer remains difficult to diagnose and treat effectively. Accordingly, there is a need in the art for improved methods for detecting and treating

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such cancers. The present invention fulfills these needs and further provides other related advantages.

#### SUMMARY OF THE INVENTION

Briefly stated, the present invention provides compositions and methods for the diagnosis and therapy of cancer, such as prostate cancer. In one aspect, the present invention provides polypeptides comprising at least a portion of a prostate tumor protein, or a variant thereof. Certain portions and other variants are immunogenic, such that the ability of the variant to react with antigen-specific antisera is not substantially diminished. Within certain embodiments, the polypeptide comprises at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of: (a) sequences recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and (c) complements of any of the sequence of (a) or (b). In certain specific embodiments, such a polypeptide comprises at least a portion, or variant thereof, of a tumor protein that includes an amino acid sequence selected from the group consisting of sequences recited in any one of SEQ ID NO: 112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

The present invention further provides polynucleotides that encode a polypeptide as described above, or a portion thereof (such as a portion encoding at least 15 amino acid residues of a prostate tumor protein), expression vectors comprising such polynucleotides and host cells transformed or transfected with such expression vectors.

Within other aspects, the present invention provides pharmaceutical compositions comprising a polypeptide or polynucleotide as described above and a physiologically acceptable carrier.

Within a related aspect of the present invention, vaccines are provided. Such vaccines comprise a polypeptide or polynucleotide as described above and a non-specific immune response enhancer.

The present invention further provides pharmaceutical compositions that comprise: (a) an antibody or antigen-binding fragment thereof that specifically binds to a prostate tumor protein; and (b) a physiologically acceptable carrier.

Within further aspects, the present invention provides pharmaceutical compositions comprising: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a pharmaceutically acceptable carrier or excipient. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B cells.

Within related aspects, vaccines are provided that comprise: (a) an antigen presenting cell that expresses a polypeptide as described above and (b) a non-specific immune response enhancer.

The present invention further provides, in other aspects, fusion proteins that comprise at least one polypeptide as described above, as well as polynucleotides encoding such fusion proteins.

Within related aspects, pharmaceutical compositions comprising a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a physiologically acceptable carrier are provided.

Vaccines are further provided, within other aspects, that comprise a fusion protein, or a polynucleotide encoding a fusion protein, in combination with a non-specific immune response enhancer.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient a pharmaceutical composition or vaccine as recited above.

The present invention further provides, within other aspects, methods for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the protein from the sample.

Within related aspects, methods are provided for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated as described above.

Methods are further provided, within other aspects, for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of: (i) a polypeptide as described above; (ii) a polypucleotide encoding such a polypeptide; and/or (iii) an antigen presenting cell that expresses such a polypeptide; under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells. Isolated T cell populations comprising T cells prepared as described above are also provided.

Within further aspects, the present invention provides methods for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population as described above.

The present invention further provides methods for inhibiting the development of a cancer in a patient, comprising the steps of: (a) incubating CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient with one or more of: (i) a polypeptide comprising at least an immunogenic portion of a prostate tumor protein; (ii) a polynucleotide encoding such a polypeptide; and (iii) an antigen-presenting cell that expressed such a polypeptide; and (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient. Proliferated cells may, but need not, be cloned prior to administration to the patient.

Within further aspects, the present invention provides methods for determining the presence or absence of a cancer in a patient, comprising: (a) contacting a biological sample obtained from a patient with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and (c) comparing the amount of polypeptide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within preferred embodiments, the binding agent is an antibody, more preferably a monoclonal antibody. The cancer may be prostate cancer.

The present invention also provides, within other aspects, methods for monitoring the progression of a cancer in a patient. Such methods comprise the steps of: (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a polypeptide as recited above; (b) detecting in the sample an amount of polypeptide that binds to the binding agent; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polypeptide detected in step (c) with the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

The present invention further provides, within other aspects, methods for determining the presence or absence of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample a level of a polynucleotide, preferably mRNA, that hybridizes to the oligonucleotide; and (c) comparing the level of polynucleotide that hybridizes to the oligonucleotide with a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient. Within certain embodiments, the amount of mRNA is detected via polymerase chain reaction using, for example, at least one oligonucleotide primer that hybridizes to a polynucleotide encoding a polypeptide as recited above, or a complement of such a polynucleotide. Within other embodiments, the amount of mRNA is detected using a hybridization technique, employing an oligonucleotide probe that hybridizes to a polynucleotide that encodes a polypeptide as recited above, or a complement of such a polynucleotide.

In related aspects, methods are provided for monitoring the progression of a cancer in a patient, comprising the steps of: (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein; (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and (d) comparing the amount of polynucleotide detected in step (c) with the amount

detected in step (b) and therefrom monitoring the progression of the cancer in the patient.

Within further aspects, the present invention provides antibodies, such as monoclonal antibodies, that bind to a polypeptide as described above, as well as diagnostic kits comprising such antibodies. Diagnostic kits comprising one or more oligonucleotide probes or primers as described above are also provided.

These and other aspects of the present invention will become apparent upon reference to the following detailed description and attached drawings. All references disclosed herein are hereby incorporated by reference in their entirety as if each was incorporated individually.

## BRIEF DESCRIPTION OF THE DRAWINGS AND SEQUENCE IDENTIFIERS

Figure 1 illustrates the ability of T cells to kill fibroblasts expressing the representative prostate tumor polypeptide P502S, as compared to control fibroblasts. The percentage lysis is shown as a series of effector:target ratios, as indicated.

Figures 2A and 2B illustrate the ability of T cells to recognize cells expressing the representative prostate tumor polypeptide P502S. In each case, the number of γ-interferon spots is shown for different numbers of responders. In Figure 2A, data is presented for fibroblasts pulsed with the P2S-12 peptide, as compared to fibroblasts pulsed with a control E75 peptide. In Figure 2B, data is presented for fibroblasts expressing P502S, as compared to fibroblasts expressing HER-2/neu.

Figure 3 represents a peptide competition binding assay showing that the P1S#10 peptide, derived from P501S, binds HLA-A2. Peptide P1S#10 inhibits HLA-A2 restricted presentation of fluM58 peptide to CTL clone D150M58 in TNF release bioassay. D150M58 CTL is specific for the HLA-A2 binding influenza matrix peptide fluM58.

Figure 4 illustrates the ability of T cell lines generated from P1S#10 immunized mice to specifically lyse P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat A2Kb targets, as compared to EGFP-transduced Jurkat A2Kb. The percent lysis is shown as a series of effector to target ratios, as indicated.

Figure 5 illustrates the ability of a T cell clone to recognize and specifically lyse Jurkat A2Kb cells expressing the representative prostate tumor polypeptide P501S, thereby demonstrating that the P1S#10 peptide may be a naturally processed epitope of the P501S polypeptide.

Figures 6A and 6B are graphs illustrating the specificity of a CD8<sup>+</sup> cell line (3A-1) for a representative prostate tumor antigen (P501S). Figure 6A shows the results of a <sup>51</sup>Cr release assay. The percent specific lysis is shown as a series of effector:target ratios, as indicated. Figure 6B shows the production of interferongamma by 3A-1 cells stimulated with autologous B-LCL transduced with P501S, at varying effector:target rations as indicated.

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SEQ ID NO: 259 is the determined cDNA sequence for JP1B1 SEQ ID NO: 260 is the determined cDNA sequence for JP1B2 SEQ ID NO: 261 is the determined cDNA sequence for JP1D3 SEQ ID NO: 262 is the determined cDNA sequence for JP1A4 SEQ ID NO: 263 is the determined cDNA sequence for JP1F5 SEQ ID NO: 264 is the determined cDNA sequence for JP1E6 SEQ ID NO: 265 is the determined cDNA sequence for JP1D6 SEQ ID NO: 266 is the determined cDNA sequence for JP1B5 SEQ ID NO: 267 is the determined eDNA sequence for JP1A6 SEQ ID NO: 268 is the determined cDNA sequence for JP1E8 SEQ ID NO: 269 is the determined cDNA sequence for JP1D7 SEQ ID NO: 270 is the determined cDNA sequence for JP1D9 SEQ ID NO: 271 is the determined cDNA sequence for JP1C10 SEQ ID NO: 272 is the determined cDNA sequence for JP1A9 SEQ ID NO: 273 is the determined cDNA sequence for JP1F12 SEQ ID NO: 274 is the determined cDNA sequence for JP1E12 SEQ ID NO: 275 is the determined cDNA sequence for JP1D11 SEQ ID NO: 276 is the determined cDNA sequence for JP1C11 SEQ ID NO: 277 is the determined cDNA sequence for JP1C12 SEQ ID NO: 278 is the determined cDNA sequence for JP1B12 SEQ ID NO: 279 is the determined cDNA sequence for JP1A12 SEQ ID NO: 280 is the determined cDNA sequence for JP8G2 SEQ ID NO: 281 is the determined cDNA sequence for JP8H1 SEQ ID NO: 282 is the determined cDNA sequence for JP8H2 SEQ ID NO: 283 is the determined cDNA sequence for JP8A3 SEQ ID NO: 284 is the determined cDNA sequence for JP8A4 SEQ ID NO: 285 is the determined cDNA sequence for JP8C3 SEQ ID NO: 286 is the determined cDNA sequence for JP8G4 SEQ ID NO: 287 is the determined cDNA sequence for JP8B6 SEQ ID NO: 288 is the determined cDNA sequence for JP8D6

SEQ ID NO: 289 is the determined cDNA sequence for JP8F5 SEQ ID NO: 290 is the determined cDNA sequence for JP8A8 SEQ ID NO: 291 is the determined cDNA sequence for JP8C7 SEQ'ID NO: 292 is the determined cDNA sequence for JP8D7 SEQ ID NO: 293 is the determined cDNA sequence for P8D8 SEQ ID NO: 294 is the determined cDNA sequence for JP8E7 SEQ ID NO: 295 is the determined cDNA sequence for JP8F8 SEQ ID NO: 296 is the determined cDNA sequence for JP8G8 SEQ ID NO: 297 is the determined cDNA sequence for JP8B10 SEQ ID NO: 298 is the determined cDNA sequence for JP8C10 SEQ ID NO: 299 is the determined cDNA sequence for JP8E9 SEQ ID NO: 300 is the determined cDNA sequence for JP8E10 SEQ ID NO: 301 is the determined cDNA sequence for JP8F9 SEQ ID NO: 302 is the determined cDNA sequence for JP8H9 SEQ ID NO: 303 is the determined cDNA sequence for JP8C12 SEQ ID NO: 304 is the determined cDNA sequence for JP8E11 SEQ ID NO: 305 is the determined cDNA sequence for JP8E12 SEQ ID NO: 306 is the amino acid sequence for the peptide PS2#12 SEQ ID NO: 307 is the determined cDNA sequence for P711P SEQ ID NO: 308 is the determined cDNA sequence for P712P SEQ ID NO: 309 is the determined cDNA sequence for CLONE23 SEQ ID NO: 310 is the determined cDNA sequence for P774P SEQ ID NO: 311 is the determined cDNA sequence for P775P SEQ ID NO: 312 is the determined cDNA sequence for P715P SEQ ID NO: 313 is the determined cDNA sequence for P710P SEQ ID NO: 314 is the determined cDNA sequence for P767P SEQ ID NO: 315 is the determined cDNA sequence for P768P SEQ ID NO: 316-325 are the determined cDNA sequences of previously isolated genes SEQ ID NO: 326 is the determined cDNA sequence for P703PDE5 SEQ ID NO: 327 is the predicted amino acid sequence for P703PDE5

SEQ ID NO: 328 is the determined cDNA sequence for P703P6.26

SEQ ID NO: 329 is the predicted amino acid sequence for P703P6.26

SEQ ID NO: 330 is the determined cDNA sequence for P703PX-23

SEQ ID NO: 331 is the predicted amino acid sequence for P703PX-23

SEQ ID NO: 332 is the determined full length cDNA sequence for P509S

SEQ ID NO: 333 is the determined extended cDNA sequence for P707P (also referred

to as 11-C9)

SEQ ID NO: 334 is the determined cDNA sequence for P714P

SEQ ID NO: 335 is the determined cDNA sequence for P705P (also referred to as 9-

F3)

SEQ ID NO: 336 is the predicted amino acid sequence for P705P

SEQ ID NO: 337 is the amino acid sequence of the peptide P1S#10

SEQ ID NO: 338 is the amino acid sequence of the peptide p5

SEQ ID NO: 339 is the predicted amino acid sequence of P509S

SEQ ID NO: 340 is the determined cDNA sequence for P778P

SEQ ID NO: 341 is the determined cDNA sequence for P786P

SEQ ID NO: 342 is the determined cDNA sequence for P789P

SEQ ID NO: 343 is the determined cDNA sequence for a clone showing homology to

Homo sapiens MM46 mRNA

SEQ ID NO: 344 is the determined cDNA sequence for a clone showing homology to

Homo sapiens TNF-alpha stimulated ABC protein (ABC50) mRNA

SEQ ID NO: 345 is the determined cDNA sequence for a clone showing homology to

Homo sapiens mRNA for E-cadherin

SEQ ID NO: 346 is the determined cDNA sequence for a clone showing homology to

Human nuclear-encoded mitochondrial serine hydroxymethyltransferase (SHMT)

SEQ ID NO: 347 is the determined cDNA sequence for a clone showing homology to

Homo sapiens natural resistance-associated macrophage protein2 (NRAMP2)

SEQ ID NO: 348 is the determined cDNA sequence for a clone showing homology to

Homo sapiens phosphoglucomutase-related protein (PGMRP)

SEQ ID NO: 349 is the determined cDNA sequence for a clone showing homology to

Human mRNA for proteosome subunit p40

SEQ ID NO: 350 is the determined cDNA sequence for P777P

SEQ ID NO: 351 is the determined cDNA sequence for P779P

SEQ ID NO: 352 is the determined cDNA sequence for P790P

SEQ ID NO: 353 is the determined cDNA sequence for P784P

SEQ ID NO: 354 is the determined cDNA sequence for P776P

SEQ ID NO: 355 is the determined cDNA sequence for P780P

SEQ ID NO: 356 is the determined cDNA sequence for P544S

SEQ ID NO: 357 is the determined cDNA sequence for P745S

SEQ ID NO: 358 is the determined cDNA sequence for P782P

SEQ ID NO: 359 is the determined cDNA sequence for P783P

SEQ ID NO: 360 is the determined cDNA sequence for unknown 17984

SEQ ID NO: 361 is the determined cDNA sequence for P787P

SEQ ID NO: 362 is the determined cDNA sequence for P788P

SEQ ID NO: 363 is the determined cDNA sequence for unknown 17994

SEQ ID NO: 364 is the determined cDNA sequence for P781P

SEQ ID NO: 365 is the determined cDNA sequence for P785P

SEQ ID NO: 366-375 are the determined cDNA sequences for splice variants of

B305D.

SEQ ID NO: 376 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 366.

SEQ ID NO: 377 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 372.

SEQ ID NO: 378 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 373.

SEQ ID NO: 379 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 374.

SEQ ID NO: 380 is the predicted amino acid sequence encoded by the sequence of SEQ

ID NO: 375.

SEQ ID NO: 381 is the determined cDNA sequence for B716P.

SEQ ID NO: 382 is the determined full-length cDNA sequence for P711P.

SEQ ID NO: 383 is the predicted amino acid sequence for P711P.

SEQ ID NO: 384 is the cDNA sequence for P1000C.

SEQ ID NO: 385 is the cDNA sequence for CGI-82.

SEQ ID NO:386 is the cDNA sequence for 23320.

SEQ ID NO:387 is the cDNA sequence for CGI-69.

SEQ ID NO:388 is the cDNA sequence for L-iditol-2-dehydrogenase.

SEQ ID NO:389 is the cDNA sequence for 23379.

SEQ ID NO:390 is the cDNA sequence for 23381.

SEQ ID NO:391 is the cDNA sequence for KIAA0122.

SEQ ID NO:392 is the cDNA sequence for 23399.

SEQ ID NO:393 is the cDNA sequence for a previously identified gene.

SEQ ID NO:394 is the cDNA sequence for HCLBP.

SEQ ID NO:395 is the cDNA sequence for transglutaminase.

SEQ ID NO:396 is the cDNA sequence for a previously identified gene.

SEQ ID NO:397 is the cDNA sequence for PAP.

SEQ ID NO:398 is the cDNA sequence for Ets transcription factor PDEF.

SEQ ID NO:399 is the cDNA sequence for hTGR.

SEQ ID NO:400 is the cDNA sequence for KIAA0295.

SEQ ID NO:401 is the cDNA sequence for 22545.

SEQ ID NO:402 is the cDNA sequence for 22547.

SEQ ID NO:403 is the cDNA sequence for 22548.

SEQ ID NO:404 is the cDNA sequence for 22550.

SEQ ID NO:405 is the cDNA sequence for 22551.

SEQ ID NO:406 is the cDNA sequence for 22552.

SEQ ID NO:407 is the cDNA sequence for 22553.

SEQ ID NO:408 is the cDNA sequence for 22558.

SEQ ID NO:409 is the cDNA sequence for 22562.

SEQ ID NO:410 is the cDNA sequence for 22565.

SEQ ID NO:411 is the cDNA sequence for 22567. SEQ ID NO:412 is the cDNA sequence for 22568. SEQ ID NO:413 is the cDNA sequence for 22570. SEQ ID NO:414 is the cDNA sequence for 22571. SEQ ID NO:415 is the cDNA sequence for 22572. SEQ ID NO:416 is the cDNA sequence for 22573. SEQ ID NO:417 is the cDNA sequence for 22573. SEQ ID NO:418 is the cDNA sequence for 22575. SEQ ID NO:419 is the cDNA sequence for 22580. SEQ ID NO:420 is the cDNA sequence for 22581. SEQ ID NO:421 is the cDNA sequence for 22582. SEQ ID NO:422 is the cDNA sequence for 22583. SEQ ID NO:423 is the cDNA sequence for 22584. SEQ ID NO:424 is the cDNA sequence for 22585. SEQ ID NO:425 is the cDNA sequence for 22586. SEQ ID NO:426 is the cDNA sequence for 22587. SEQ ID NO:427 is the cDNA sequence for 22588. SEQ ID NO:428 is the cDNA sequence for 22589. SEQ ID NO:429 is the cDNA sequence for 22590. SEQ ID NO:430 is the cDNA sequence for 22591. SEQ ID NO:431 is the cDNA sequence for 22592. SEQ ID NO:432 is the cDNA sequence for 22593. SEQ ID NO:433 is the cDNA sequence for 22594. SEQ ID NO:434 is the cDNA sequence for 22595. SEQ ID NO:435 is the cDNA sequence for 22596. SEQ ID NO:436 is the cDNA sequence for 22847. SEQ ID NO:437 is the cDNA sequence for 22848. SEQ ID NO:438 is the cDNA sequence for 22849. SEQ ID NO:439 is the cDNA sequence for 22851. SEQ ID NO:440 is the cDNA sequence for 22852.

SEQ ID NO:441 is the cDNA sequence for 22853.

SEQ ID NO:442 is the cDNA sequence for 22854.

SEQ ID NO:443 is the cDNA sequence for 22855.

SEQ ID NO:444 is the cDNA sequence for 22856.

SEQ ID NO:445 is the cDNA sequence for 22857.

SEQ ID NO:446 is the cDNA sequence for 23601.

SEQ ID NO:447 is the cDNA sequence for 23602.

SEQ ID NO:448 is the cDNA sequence for 23605.

SEQ ID NO:449 is the cDNA sequence for 23606.

SEQ ID NO:450 is the cDNA sequence for 23612.

SEQ ID NO:451 is the cDNA sequence for 23614.

SEQ ID NO:452 is the cDNA sequence for 23618.

SEQ ID NO:453 is the cDNA sequence for 23622.

SEQ ID NO:454 is the cDNA sequence for folate hydrolase.

SEQ ID NO:455 is the cDNA sequence for LIM protein.

SEQ ID NO:456 is the cDNA sequence for a known gene.

SEQ ID NO:457 is the cDNA sequence for a known gene.

SEQ ID NO:458 is the cDNA sequence for a previously identified gene.

SEQ ID NO:459 is the cDNA sequence for 23045.

SEQ ID NO:460 is the cDNA sequence for 23032.

SEQ ID NO:461 is the cDNA sequence for 23054.

SEQ ID NOs:462-467 are cDNA sequences for known genes.

SEQ ID NOs:468-471 are cDNA sequences for P710P.

SEQ ID NO:472 is a cDNA sequence for P1001C.

SEQ ID NO:473 is the amino acid sequence for PSMA.

SEQ ID NO:474 is the amino acid sequence for PAP.

SEQ ID NO:475 is the amino acid sequence for PSA.

SEQ ID NO:476 is the amino acid sequence for a fusion protein containing PSA, P703P and P501S.

#### DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is generally directed to compositions and methods for the therapy and diagnosis of cancer, such as prostate cancer. The compositions described herein may include prostate tumor polypeptides, polynucleotides encoding such polypeptides, binding agents such as antibodies, antigen presenting cells (APCs) and/or immune system cells (e.g., T cells). Polypeptides of the present invention generally comprise at least a portion (such as an immunogenic portion) of a prostate tumor protein or a variant thereof. A "prostate tumor protein" is a protein that is expressed in prostate tumor cells at a level that is at least two fold, and preferably at least five fold, greater than the level of expression in a normal tissue, as determined using a representative assay provided herein. Certain prostate tumor proteins are tumor proteins that react detectably (within an immunoassay, such as an ELISA or Western blot) with antisera of a patient afflicted with prostate cancer. Polynucleotides of the subject invention generally comprise a DNA or RNA sequence that encodes all or a portion of such a polypeptide, or that is complementary to such a sequence. Antibodies are generally immune system proteins, or antigen-binding fragments thereof, that are capable of binding to a polypeptide as described above. Antigen presenting cells include dendritic cells, macrophages, monocytes, fibroblasts and B-cells that express a polypeptide as described above. T cells that may be employed within such compositions are generally T cells that are specific for a polypeptide as described above.

The present invention is based on the discovery of human prostate tumor proteins. Sequences of polynucleotides encoding certain tumor proteins, or portions thereof, are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Sequences of polypeptides comprising at least a portion of a tumor protein are provided in SEQ ID NOs:112-114, 172, 176, 178, 327, 329, 331, 336, 339, 376-380 and 383.

### PROSTATE TUMOR PROTEIN POLYNUCLEOTIDES

Any polynucleotide that encodes a prostate tumor protein or a portion or other variant thereof as described herein is encompassed by the present invention. Preferred polynucleotides comprise at least 15 consecutive nucleotides, preferably at least 30 consecutive nucleotides and more preferably at least 45 consecutive nucleotides, that encode a portion of a prostate tumor protein. More preferably, a polynucleotide encodes an immunogenic portion of a prostate tumor protein. Polynucleotides complementary to any such sequences are also encompassed by the present invention. Polynucleotides may be single-stranded (coding or antisense) or double-stranded, and may be DNA (genomic, cDNA or synthetic) or RNA molecules. RNA molecules include HnRNA molecules, which contain introns and correspond to a DNA molecule in a one-to-one manner, and mRNA molecules, which do not contain introns. Additional coding or non-coding sequences may, but need not, be present within a polynucleotide of the present invention, and a polynucleotide may, but need not, be linked to other molecules and/or support materials.

Polynucleotides may comprise a native sequence (i.e., an endogenous sequence that encodes a prostate tumor protein or a portion thereof) or may comprise a variant of such a sequence. Polynucleotide variants may contain one or more substitutions, additions, deletions and/or insertions such that the immunogenicity of the encoded polypeptide is not diminished, relative to a native tumor protein. The effect on the immunogenicity of the encoded polypeptide may generally be assessed as described herein. Variants preferably exhibit at least about 70% identity, more preferably at least about 80% identity and most preferably at least about 90% identity to a polynucleotide sequence that encodes a native prostate tumor protein or a portion thereof.

Two polynucleotide or polypeptide sequences are said to be "identical" if the sequence of nucleotides or amino acids in the two sequences is the same when aligned for maximum correspondence as described below. Comparisons between two sequences are typically performed by comparing the sequences over a comparison window to identify and compare local regions of sequence similarity. A "comparison window" as used herein, refers to a segment of at least about 20 contiguous positions,

usually 30 to about 75, 40 to about 50, in which a sequence may be compared to a reference sequence of the same number of contiguous positions after the two sequences are optimally aligned.

Optimal alignment of sequences for comparison may be conducted using the Megalign program in the Lasergene suite of bioinformatics software (DNASTAR, Inc., Madison, WI), using default parameters. This program embodies several alignment schemes described in the following references: Dayhoff, M.O. (1978) A model of evolutionary change in proteins – Matrices for detecting distant relationships. In Dayhoff, M.O. (ed.) Atlas of Protein Sequence and Structure, National Biomedical Research Foundation, Washington DC Vol. 5, Suppl. 3, pp. 345-358; Hein J. (1990) Unified Approach to Alignment and Phylogenes pp. 626-645 *Methods in Enzymology* vol. 183, Academic Press, Inc., San Diego, CA; Higgins, D.G. and Sharp, P.M. (1989) *CABIOS* 5:151-153; Myers, E.W. and Muller W. (1988) *CABIOS* 4:11-17; Robinson, E.D. (1971) *Comb. Theor 11*:105; Santou, N. Nes, M. (1987) *Mol. Biol. Evol.* 4:406-425; Sneath, P.H.A. and Sokal, R.R. (1973) *Numerical Taxonomy – the Principles and Practice of Numerical Taxonomy*, Freeman Press, San Francisco, CA; Wilbur, W.J. and Lipman, D.J. (1983) *Proc. Natl. Acad., Sci. USA* 80:726-730.

Preferably, the "percentage of sequence identity" is determined by comparing two optimally aligned sequences over a window of comparison of at least 20 positions, wherein the portion of the polynucleotide or polypeptide sequence in the comparison window may comprise additions or deletions (*i.e.*, gaps) of 20 percent or less, usually 5 to 15 percent, or 10 to 12 percent, as compared to the reference sequences (which does not comprise additions or deletions) for optimal alignment of the two sequences. The percentage is calculated by determining the number of positions at which the identical nucleic acid bases or amino acid residue occurs in both sequences to yield the number of matched positions, dividing the number of matched positions by the total number of positions in the reference sequence (*i.e.*, the window size) and multiplying the results by 100 to yield the percentage of sequence identity.

Variants may also, or alternatively, be substantially homologous to a native gene, or a portion or complement thereof. Such polynucleotide variants are

capable of hybridizing under moderately stringent conditions to a naturally occurring DNA sequence encoding a native prostate tumor protein (or a complementary sequence). Suitable moderately stringent conditions include prewashing in a solution of 5 X SSC, 0.5% SDS, 1.0 mM EDTA (pH 8.0); hybridizing at 50°C-65°C, 5 X SSC, overnight; followed by washing twice at 65°C for 20 minutes with each of 2X, 0.5X and 0.2X SSC containing 0.1% SDS.

It will be appreciated by those of ordinary skill in the art that, as a result of the degeneracy of the genetic code, there are many nucleotide sequences that encode a polypeptide as described herein. Some of these polynucleotides bear minimal homology to the nucleotide sequence of any native gene. Nonetheless, polynucleotides that vary due to differences in codon usage are specifically contemplated by the present invention. Further, alleles of the genes comprising the polynucleotide sequences provided herein are within the scope of the present invention. Alleles are endogenous genes that are altered as a result of one or more mutations, such as deletions, additions and/or substitutions of nucleotides. The resulting mRNA and protein may, but need not, have an altered structure or function. Alleles may be identified using standard techniques (such as hybridization, amplification and/or database sequence comparison).

Polynucleotides may be prepared using any of a variety of techniques. For example, a polynucleotide may be identified, as described in more detail below, by screening a microarray of cDNAs for tumor-associated expression (*i.e.*, expression that is at least five fold greater in a prostate tumor than in normal tissue, as determined using a representative assay provided herein). Such screens may be performed using a Synteni microarray (Palo Alto, CA) according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Alternatively, polypeptides may be amplified from cDNA prepared from cells expressing the proteins described herein, such as prostate tumor cells. Such polynucleotides may be amplified via polymerase chain reaction (PCR). For this approach, sequence-specific primers may be designed based on the sequences provided herein, and may be purchased or synthesized.

An amplified portion may be used to isolate a full length gene from a suitable library (e.g., a prostate tumor cDNA library) using well known techniques. Within such techniques, a library (cDNA or genomic) is screened using one or more polynucleotide probes or primers suitable for amplification. Preferably, a library is size-selected to include larger molecules. Random primed libraries may also be preferred for identifying 5' and upstream regions of genes. Genomic libraries are preferred for obtaining introns and extending 5' sequences.

For hybridization techniques, a partial sequence may be labeled (e.g., by nick-translation or end-labeling with <sup>32</sup>P) using well known techniques. A bacterial or bacteriophage library is then screened by hybridizing filters containing denatured bacterial colonies (or lawns containing phage plaques) with the labeled probe (see Sambrook et al., Molecular Cloning: A Laboratory Manual, Cold Spring Harbor Laboratories, Cold Spring Harbor, NY, 1989). Hybridizing colonies or plaques are selected and expanded, and the DNA is isolated for further analysis. cDNA clones may be analyzed to determine the amount of additional sequence by, for example, PCR using a primer from the partial sequence and a primer from the vector. Restriction maps and partial sequences may be generated to identify one or more overlapping clones. The complete sequence may then be determined using standard techniques, which may involve generating a series of deletion clones. The resulting overlapping sequences are then assembled into a single contiguous sequence. A full length cDNA molecule can be generated by ligating suitable fragments, using well known techniques.

Alternatively, there are numerous amplification techniques for obtaining a full length coding sequence from a partial cDNA sequence. Within such techniques, amplification is generally performed via PCR. Any of a variety of commercially available kits may be used to perform the amplification step. Primers may be designed using, for example, software well known in the art. Primers are preferably 22-30 nucleotides in length, have a GC content of at least 50% and anneal to the target sequence at temperatures of about 68°C to 72°C. The amplified region may be sequenced as described above, and overlapping sequences assembled into a contiguous sequence.

One such amplification technique is inverse PCR (see Triglia et al., Nucl. Acids Res. 16:8186, 1988), which uses restriction enzymes to generate a fragment in the known region of the gene. The fragment is then circularized by intramolecular ligation and used as a template for PCR with divergent primers derived from the known region. Within an alternative approach, sequences adjacent to a partial sequence may be retrieved by amplification with a primer to a linker sequence and a primer specific to a known region. The amplified sequences are typically subjected to a second round of amplification with the same linker primer and a second primer specific to the known A variation on this procedure, which employs two primers that initiate extension in opposite directions from the known sequence, is described in WO 96/38591. Another such technique is known as "rapid amplification of cDNA ends" or RACE. This technique involves the use of an internal primer and an external primer, which hybridizes to a polyA region or vector sequence, to identify sequences that are 5' and 3' of a known sequence. Additional techniques include capture PCR (Lagerstrom et al., PCR Methods Applic. 1:111-19, 1991) and walking PCR (Parker et al., Nucl. Acids. Res. 19:3055-60, 1991). Other methods employing amplification may also be employed to obtain a full length cDNA sequence.

In certain instances, it is possible to obtain a full length cDNA sequence by analysis of sequences provided in an expressed sequence tag (EST) database, such as that available from GenBank. Searches for overlapping ESTs may generally be performed using well known programs (e.g., NCBI BLAST searches), and such ESTs may be used to generate a contiguous full length sequence.

Certain nucleic acid sequences of cDNA molecules encoding at least a portion of a prostate tumor protein are provided in SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472. Isolation of these polynucleotides is described below. Each of these prostate tumor proteins was overexpressed in prostate tumor tissue.

Polynucleotide variants may generally be prepared by any method known in the art, including chemical synthesis by, for example, solid phase phosphoramidite chemical synthesis. Modifications in a polynucleotide sequence may

also be introduced using standard mutagenesis techniques, such as oligonucleotide-directed site-specific mutagenesis (see Adelman et al., DNA 2:183, 1983). Alternatively, RNA molecules may be generated by in vitro or in vivo transcription of DNA sequences encoding a prostate tumor protein, or portion thereof, provided that the DNA is incorporated into a vector with a suitable RNA polymerase promoter (such as T7 or SP6). Certain portions may be used to prepare an encoded polypeptide, as described herein. In addition, or alternatively, a portion may be administered to a patient such that the encoded polypeptide is generated in vivo (e.g., by transfecting antigen-presenting cells, such as dendritic cells, with a cDNA construct encoding a prostate tumor polypeptide, and administering the transfected cells to the patient).

A portion of a sequence complementary to a coding sequence (*i.e.*, an antisense polynucleotide) may also be used as a probe or to modulate gene expression. cDNA constructs that can be transcribed into antisense RNA may also be introduced into cells of tissues to facilitate the production of antisense RNA. An antisense polynucleotide may be used, as described herein, to inhibit expression of a tumor protein. Antisense technology can be used to control gene expression through triple-helix formation, which compromises the ability of the double helix to open sufficiently for the binding of polymerases, transcription factors or regulatory molecules (*see* Gee et al., *In* Huber and Carr, *Molecular and Immunologic Approaches*, Futura Publishing Co. (Mt. Kisco, NY; 1994)). Alternatively, an antisense molecule may be designed to hybridize with a control region of a gene (*e.g.*, promoter, enhancer or transcription initiation site), and block transcription of the gene; or to block translation by inhibiting binding of a transcript to ribosomes.

A portion of a coding sequence, or of a complementary sequence, may also be designed as a probe or primer to detect gene expression. Probes may be labeled with a variety of reporter groups, such as radionuclides and enzymes, and are preferably at least 10 nucleotides in length, more preferably at least 20 nucleotides in length and still more preferably at least 30 nucleotides in length. Primers, as noted above, are preferably 22-30 nucleotides in length.

Any polynucleotide may be further modified to increase stability *in vivo*. Possible modifications include, but are not limited to, the addition of flanking sequences at the 5' and/or 3' ends; the use of phosphorothioate or 2' O-methyl rather than phosphodiesterase linkages in the backbone; and/or the inclusion of nontraditional bases such as inosine, queosine and wybutosine, as well as acetyl- methyl-, thio- and other modified forms of adenine, cytidine, guanine, thymine and uridine.

Nucleotide sequences as described herein may be joined to a variety of other nucleotide sequences using established recombinant DNA techniques. For example, a polynucleotide may be cloned into any of a variety of cloning vectors, including plasmids, phagemids, lambda phage derivatives and cosmids. Vectors of particular interest include expression vectors, replication vectors, probe generation vectors and sequencing vectors. In general, a vector will contain an origin of replication functional in at least one organism, convenient restriction endonuclease sites and one or more selectable markers. Other elements will depend upon the desired use, and will be apparent to those of ordinary skill in the art.

Within certain embodiments, polynucleotides may be formulated so as to permit entry into a cell of a mammal, and expression therein. Such formulations are particularly useful for therapeutic purposes, as described below. Those of ordinary skill in the art will appreciate that there are many ways to achieve expression of a polynucleotide in a target cell, and any suitable method may be employed. For example, a polynucleotide may be incorporated into a viral vector such as, but not limited to, adenovirus, adeno-associated virus, retrovirus, or vaccinia or other pox virus (e.g., avian pox virus). Techniques for incorporating DNA into such vectors are well known to those of ordinary skill in the art. A retroviral vector may additionally transfer or incorporate a gene for a selectable marker (to aid in the identification or selection of transduced cells) and/or a targeting moiety, such as a gene that encodes a ligand for a receptor on a specific target cell, to render the vector target specific. Targeting may also be accomplished using an antibody, by methods known to those of ordinary skill in the art.

Other formulations for therapeutic purposes include colloidal dispersion systems, such as macromolecule complexes, nanocapsules, microspheres, beads, and lipid-based systems including oil-in-water emulsions, micelles, mixed micelles, and liposomes. A preferred colloidal system for use as a delivery vehicle *in vitro* and *in vivo* is a liposome (*i.e.*, an artificial membrane vesicle). The preparation and use of such systems is well known in the art.

#### PROSTATE TUMOR POLYPEPTIDES

Within the context of the present invention, polypeptides may comprise at least an immunogenic portion of a prostate tumor protein or a variant thereof, as described herein. As noted above, a "prostate tumor protein" is a protein that is expressed by prostate tumor cells. Proteins that are prostate tumor proteins also react detectably within an immunoassay (such as an ELISA) with antisera from a patient with prostate cancer. Polypeptides as described herein may be of any length. Additional sequences derived from the native protein and/or heterologous sequences may be present, and such sequences may (but need not) possess further immunogenic or antigenic properties.

An "immunogenic portion," as used herein is a portion of a protein that is recognized (*i.e.*, specifically bound) by a B-cell and/or T-cell surface antigen receptor. Such immunogenic portions generally comprise at least 5 amino acid residues, more preferably at least 10, and still more preferably at least 20 amino acid residues of a prostate tumor protein or a variant thereof. Certain preferred immunogenic portions include peptides in which an N-terminal leader sequence and/or transmembrane domain have been deleted. Other preferred immunogenic portions may contain a small N- and/or C-terminal deletion (*e.g.*, 1-30 amino acids, preferably 5-15 amino acids), relative to the mature protein.

Immunogenic portions may generally be identified using well known techniques, such as those summarized in Paul, *Fundamental Immunology*, 3rd ed., 243-247 (Raven Press, 1993) and references cited therein. Such techniques include screening polypeptides for the ability to react with antigen-specific antibodies, antisera

and/or T-cell lines or clones. As used herein, antisera and antibodies are "antigen-specific" if they specifically bind to an antigen (*i.e.*, they react with the protein in an ELISA or other immunoassay, and do not react detectably with unrelated proteins). Such antisera and antibodies may be prepared as described herein, and using well known techniques. An immunogenic portion of a native prostate tumor protein is a portion that reacts with such antisera and/or T-cells at a level that is not substantially less than the reactivity of the full length polypeptide (*e.g.*, in an ELISA and/or T-cell reactivity assay). Such immunogenic portions may react within such assays at a level that is similar to or greater than the reactivity of the full length polypeptide. Such screens may generally be performed using methods well known to those of ordinary skill in the art, such as those described in Harlow and Lane, *Antibodies: A Laboratory Manual*, Cold Spring Harbor Laboratory, 1988. For example, a polypeptide may be immobilized on a solid support and contacted with patient sera to allow binding of antibodies within the sera to the immobilized polypeptide. Unbound sera may then be removed and bound antibodies detected using, for example, <sup>125</sup>I-labeled Protein A.

As noted above, a composition may comprise a variant of a native prostate tumor protein. A polypeptide "variant," as used herein, is a polypeptide that differs from a native prostate tumor protein in one or more substitutions, deletions, additions and/or insertions, such that the immunogenicity of the polypeptide is not substantially diminished. In other words, the ability of a variant to react with antigenspecific antisera may be enhanced or unchanged, relative to the native protein, or may be diminished by less than 50%, and preferably less than 20%, relative to the native protein. Such variants may generally be identified by modifying one of the above polypeptide sequences and evaluating the reactivity of the modified polypeptide with antigen-specific antibodies or antisera as described herein. Preferred variants include those in which one or more portions, such as an N-terminal leader sequence or transmembrane domain, have been removed. Other preferred variants include variants in which a small portion (e.g., 1-30 amino acids, preferably 5-15 amino acids) has been removed from the N- and/or C-terminal of the mature protein. Polypeptide variants preferably exhibit at least about 70%, more preferably at least about 90% and most

preferably at least about 95% identity (determined as described above) to the identified polypeptides.

Preferably, a variant contains conservative substitutions. Α "conservative substitution" is one in which an amino acid is substituted for another amino acid that has similar properties, such that one skilled in the art of peptide chemistry would expect the secondary structure and hydropathic nature of the polypeptide to be substantially unchanged. Amino acid substitutions may generally be made on the basis of similarity in polarity, charge, solubility, hydrophobicity, hydrophilicity and/or the amphipathic nature of the residues. For example, negatively charged amino acids include aspartic acid and glutamic acid; positively charged amino acids include lysine and arginine; and amino acids with uncharged polar head groups having similar hydrophilicity values include leucine, isoleucine and valine; glycine and alanine; asparagine and glutamine; and serine, threonine, phenylalanine and tyrosine. Other groups of amino acids that may represent conservative changes include: (1) ala, pro, gly, glu, asp, gln, asn, ser, thr; (2) cys, ser, tyr, thr; (3) val, ile, leu, met, ala, phe; (4) lys, arg, his; and (5) phe, tyr, trp, his. A variant may also, or alternatively, contain nonconservative changes. In a preferred embodiment, variant polypeptides differ from a native sequence by substitution, deletion or addition of five amino acids or fewer. Variants may also (or alternatively) be modified by, for example, the deletion or addition of amino acids that have minimal influence on the immunogenicity, secondary structure and hydropathic nature of the polypeptide.

As noted above, polypeptides may comprise a signal (or leader) sequence at the N-terminal end of the protein which co-translationally or post-translationally directs transfer of the protein. The polypeptide may also be conjugated to a linker or other sequence for ease of synthesis, purification or identification of the polypeptide (e.g., poly-His), or to enhance binding of the polypeptide to a solid support. For example, a polypeptide may be conjugated to an immunoglobulin Fc region.

Polypeptides may be prepared using any of a variety of well known techniques. Recombinant polypeptides encoded by DNA sequences as described above may be readily prepared from the DNA sequences using any of a variety of expression

vectors known to those of ordinary skill in the art. Expression may be achieved in any appropriate host cell that has been transformed or transfected with an expression vector containing a DNA molecule that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast and higher eukaryotic cells. Preferably, the host cells employed are *E. coli*, yeast or a mammalian cell line such as COS or CHO. Supernatants from suitable host/vector systems which secrete recombinant protein or polypeptide into culture media may be first concentrated using a commercially available filter. Following concentration, the concentrate may be applied to a suitable purification matrix such as an affinity matrix or an ion exchange resin. Finally, one or more reverse phase HPLC steps can be employed to further purify a recombinant polypeptide.

Portions and other variants having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may also be generated by synthetic means, using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. See Merrifield, J. Am. Chem. Soc. 85:2149-2146, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems Division (Foster City, CA), and may be operated according to the manufacturer's instructions.

Within certain specific embodiments, a polypeptide may be a fusion protein that comprises multiple polypeptides as described herein, or that comprises at least one polypeptide as described herein and an unrelated sequence, such as a known tumor protein. A fusion partner may, for example, assist in providing T helper epitopes (an immunological fusion partner), preferably T helper epitopes recognized by humans, or may assist in expressing the protein (an expression enhancer) at higher yields than the native recombinant protein. Certain preferred fusion partners are both immunological and expression enhancing fusion partners. Other fusion partners may be selected so as to increase the solubility of the protein or to enable the protein to be

targeted to desired intracellular compartments. Still further fusion partners include affinity tags, which facilitate purification of the protein.

In certain embodiments, the present invention provides fusion proteins comprising a polypeptide disclosed herein together with at least one of the following known prostate antigens: prostate specific antigen (PSA); prostatic acid phosphatase (PAP); and prostate specific membrane antigen (PSMA). The protein sequences for PSMA, PAP and PSA are provided in SEQ ID NO: 473-475, respectively. In certain embodiments, the fusion proteins of the present invention comprise PSA, PAP and/or PSMA in combination with one or more of the following the inventive antigens: P501S (amino acid sequence provided in SEQ ID NO: 113); P703P (amino acid sequences provided in SEQ ID NO: 327, 329, 331); P704P (cDNA sequence provided in SEQ ID NO: 67); P712P (cDNA sequence provided in SEQ ID NO: 308); P775P (cDNA sequence provided in SEQ ID NO: 311); P776P (cDNA sequence provided in SEQ ID NO: 354); P790P (cDNA sequence provided in SEQ ID NO: 352). The amino acid sequence of a fusion protein of PSA, P703P and P501S is provided in SEQ ID NO: 476. In preferred embodiments, the inventive fusion proteins comprise one of the following combinations of antigens: PSA and P703P; PSA and P501S; PAP and P703P; PAP and P501S; PSMA and P703P; PSMA and P501S; PSA, PAP and P703P; PSA, PAP and P501S; PSA, PAP, PSMA and P703P, PSA, PAP, PSMA and P501S. One of skill in the art will appreciate that the order of polypeptides within a fusion protein can be altered without substantially changing the therapeutic, prophylactic or diagnostic properties of the fusion protein.

The fusion proteins described above are more immunogenic and will be effective in a greater number of prostate cancer patients than any of the individual components alone. The use of multiple antigens in the form of a fusion protein also lessens the likelihood of immunologic escape.

Fusion proteins may generally be prepared using standard techniques, including chemical conjugation. Preferably, a fusion protein is expressed as a recombinant protein, allowing the production of increased levels, relative to a non-fused protein, in an expression system. Briefly, DNA sequences encoding the polypeptide

components may be assembled separately, and ligated into an appropriate expression vector. The 3' end of the DNA sequence encoding one polypeptide component is ligated, with or without a peptide linker, to the 5' end of a DNA sequence encoding the second polypeptide component so that the reading frames of the sequences are in phase. This permits translation into a single fusion protein that retains the biological activity of both component polypeptides.

A peptide linker sequence may be employed to separate the first and the second polypeptide components by a distance sufficient to ensure that each polypeptide folds into its secondary and tertiary structures. Such a peptide linker sequence is incorporated into the fusion protein using standard techniques well known in the art. Suitable peptide linker sequences may be chosen based on the following factors: (1) their ability to adopt a flexible extended conformation; (2) their inability to adopt a secondary structure that could interact with functional epitopes on the first and second polypeptides; and (3) the lack of hydrophobic or charged residues that might react with the polypeptide functional epitopes. Preferred peptide linker sequences contain Gly, Asn and Ser residues. Other near neutral amino acids, such as Thr and Ala may also be used in the linker sequence. Amino acid sequences which may be usefully employed as linkers include those disclosed in Maratea et al., Gene 40:39-46, 1985; Murphy et al., Proc. Natl. Acad. Sci. USA 83:8258-8262, 1986; U.S. Patent No. 4,935,233 and U.S. Patent No. 4,751,180. The linker sequence may generally be from 1 to about 50 amino acids in length. Linker sequences are not required when the first and second polypeptides have non-essential N-terminal amino acid regions that can be used to separate the functional domains and prevent steric interference.

The ligated DNA sequences are operably linked to suitable transcriptional or translational regulatory elements. The regulatory elements responsible for expression of DNA are located only 5' to the DNA sequence encoding the first polypeptides. Similarly, stop codons required to end translation and transcription termination signals are only present 3' to the DNA sequence encoding the second polypeptide.

Fusion proteins are also provided that comprise a polypeptide of the present invention together with an unrelated immunogenic protein. Preferably the immunogenic protein is capable of eliciting a recall response. Examples of such proteins include tetanus, tuberculosis and hepatitis proteins (see, for example, Stoute et al. New Engl. J. Med., 336:86-91, 1997).

Within preferred embodiments, an immunological fusion partner is derived from protein D, a surface protein of the gram-negative bacterium Haemophilus influenza B (WO 91/18926). Preferably, a protein D derivative comprises approximately the first third of the protein (e.g., the first N-terminal 100-110 amino acids), and a protein D derivative may be lipidated. Within certain preferred embodiments, the first 109 residues of a Lipoprotein D fusion partner is included on the N-terminus to provide the polypeptide with additional exogenous T-cell epitopes and to increase the expression level in E. coli (thus functioning as an expression enhancer). The lipid tail ensures optimal presentation of the antigen to antigen presenting cells. Other fusion partners include the non-structural protein from influenzae virus, NS1 (hemaglutinin). Typically, the N-terminal 81 amino acids are used, although different fragments that include T-helper epitopes may be used.

In another embodiment, the immunological fusion partner is the protein known as LYTA, or a portion thereof (preferably a C-terminal portion). LYTA is derived from *Streptococcus pneumoniae*, which synthesizes an N-acetyl-L-alanine amidase known as amidase LYTA (encoded by the LytA gene; *Gene 43*:265-292, 1986). LYTA is an autolysin that specifically degrades certain bonds in the peptidoglycan backbone. The C-terminal domain of the LYTA protein is responsible for the affinity to the choline or to some choline analogues such as DEAE. This property has been exploited for the development of *E. coli* C-LYTA expressing plasmids useful for expression of fusion proteins. Purification of hybrid proteins containing the C-LYTA fragment at the amino terminus has been described (*see Biotechnology 10:795-798*, 1992). Within a preferred embodiment, a repeat portion of LYTA may be incorporated into a fusion protein. A repeat portion is found in the C-

terminal region starting at residue 178. A particularly preferred repeat portion incorporates residues 188-305.

In general, polypeptides (including fusion proteins) and polynucleotides as described herein are isolated. An "isolated" polypeptide or polynucleotide is one that is removed from its original environment. For example, a naturally-occurring protein is isolated if it is separated from some or all of the coexisting materials in the natural system. Preferably, such polypeptides are at least about 90% pure, more preferably at least about 95% pure and most preferably at least about 99% pure. A polynucleotide is considered to be isolated if, for example, it is cloned into a vector that is not a part of the natural environment.

#### **BINDING AGENTS**

The present invention further provides agents, such as antibodies and antigen-binding fragments thereof, that specifically bind to a prostate tumor protein. As used herein, an antibody, or antigen-binding fragment thereof, is said to "specifically bind" to a prostate tumor protein if it reacts at a detectable level (within, for example, an ELISA) with a prostate tumor protein, and does not react detectably with unrelated proteins under similar conditions. As used herein, "binding" refers to a noncovalent association between two separate molecules such that a complex is formed. The ability to bind may be evaluated by, for example, determining a binding constant for the formation of the complex. The binding constant is the value obtained when the concentration of the complex is divided by the product of the component concentrations. In general, two compounds are said to "bind," in the context of the present invention, when the binding constant for complex formation exceeds about 10<sup>3</sup> L/mol. The binding constant may be determined using methods well known in the art.

Binding agents may be further capable of differentiating between patients with and without a cancer, such as prostate cancer, using the representative assays provided herein. In other words, antibodies or other binding agents that bind to a prostate tumor protein will generate a signal indicating the presence of a cancer in at least about 20% of patients with the disease, and will generate a negative signal

indicating the absence of the disease in at least about 90% of individuals without the cancer. To determine whether a binding agent satisfies this requirement, biological samples (e.g., blood, sera, urine and/or tumor biopsies) from patients with and without a cancer (as determined using standard clinical tests) may be assayed as described herein for the presence of polypeptides that bind to the binding agent. It will be apparent that a statistically significant number of samples with and without the disease should be assayed. Each binding agent should satisfy the above criteria; however, those of ordinary skill in the art will recognize that binding agents may be used in combination to improve sensitivity.

Any agent that satisfies the above requirements may be a binding agent. For example, a binding agent may be a ribosome, with or without a peptide component, an RNA molecule or a polypeptide. In a preferred embodiment, a binding agent is an antibody or an antigen-binding fragment thereof. Antibodies may be prepared by any of a variety of techniques known to those of ordinary skill in the art. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, antibodies can be produced by cell culture techniques, including the generation of monoclonal antibodies as described herein, or via transfection of antibody genes into suitable bacterial or mammalian cell hosts, in order to allow for the production of recombinant antibodies. In one technique, an immunogen comprising the polypeptide is initially injected into any of a wide variety of mammals (e.g., mice, rats, rabbits, sheep or goats). In this step, the polypeptides of this invention may serve as the immunogen without modification. Alternatively, particularly for relatively short polypeptides, a superior immune response may be elicited if the polypeptide is joined to a carrier protein, such as bovine serum albumin or keyhole limpet hemocyanin. The immunogen is injected into the animal host, preferably according to a predetermined schedule incorporating one or more booster immunizations, and the animals are bled periodically. Polyclonal antibodies specific for the polypeptide may then be purified from such antisera by, for example, affinity chromatography using the polypeptide coupled to a suitable solid support.

Monoclonal antibodies specific for an antigenic polypeptide of interest may be prepared, for example, using the technique of Kohler and Milstein, Eur. J. Immunol. 6:511-519, 1976, and improvements thereto. Briefly, these methods involve the preparation of immortal cell lines capable of producing antibodies having the desired specificity (i.e., reactivity with the polypeptide of interest). Such cell lines may be produced, for example, from spleen cells obtained from an animal immunized as described above. The spleen cells are then immortalized by, for example, fusion with a myeloma cell fusion partner, preferably one that is syngeneic with the immunized animal. A variety of fusion techniques may be employed. For example, the spleen cells and myeloma cells may be combined with a nonionic detergent for a few minutes and then plated at low density on a selective medium that supports the growth of hybrid cells, but not myeloma cells. A preferred selection technique uses HAT (hypoxanthine, aminopterin, thymidine) selection. After a sufficient time, usually about 1 to 2 weeks, colonies of hybrids are observed. Single colonies are selected and their culture supernatants tested for binding activity against the polypeptide. Hybridomas having high reactivity and specificity are preferred.

Monoclonal antibodies may be isolated from the supernatants of growing hybridoma colonies. In addition, various techniques may be employed to enhance the yield, such as injection of the hybridoma cell line into the peritoneal cavity of a suitable vertebrate host, such as a mouse. Monoclonal antibodies may then be harvested from the ascites fluid or the blood. Contaminants may be removed from the antibodies by conventional techniques, such as chromatography, gel filtration, precipitation, and extraction. The polypeptides of this invention may be used in the purification process in, for example, an affinity chromatography step.

Within certain embodiments, the use of antigen-binding fragments of antibodies may be preferred. Such fragments include Fab fragments, which may be prepared using standard techniques. Briefly, immunoglobulins may be purified from rabbit serum by affinity chromatography on Protein A bead columns (Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988) and digested

by papain to yield Fab and Fc fragments. The Fab and Fc fragments may be separated by affinity chromatography on protein A bead columns.

Monoclonal antibodies of the present invention may be coupled to one or more therapeutic agents. Suitable agents in this regard include radionuclides, differentiation inducers, drugs, toxins, and derivatives thereof. Preferred radionuclides include <sup>90</sup>Y, <sup>123</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>186</sup>Re, <sup>188</sup>Re, <sup>211</sup>At, and <sup>212</sup>Bi. Preferred drugs include methotrexate, and pyrimidine and purine analogs. Preferred differentiation inducers include phorbol esters and butyric acid. Preferred toxins include ricin, abrin, diptheria toxin, cholera toxin, gelonin, Pseudomonas exotoxin, Shigella toxin, and pokeweed antiviral protein.

A therapeutic agent may be coupled (e.g., covalently bonded) to a suitable monoclonal antibody either directly or indirectly (e.g., via a linker group). A direct reaction between an agent and an antibody is possible when each possesses a substituent capable of reacting with the other. For example, a nucleophilic group, such as an amino or sulfhydryl group, on one may be capable of reacting with a carbonyl-containing group, such as an anhydride or an acid halide, or with an alkyl group containing a good leaving group (e.g., a halide) on the other.

Alternatively, it may be desirable to couple a therapeutic agent and an antibody via a linker group. A linker group can function as a spacer to distance an antibody from an agent in order to avoid interference with binding capabilities. A linker group can also serve to increase the chemical reactivity of a substituent on an agent or an antibody, and thus increase the coupling efficiency. An increase in chemical reactivity may also facilitate the use of agents, or functional groups on agents, which otherwise would not be possible.

It will be evident to those skilled in the art that a variety of bifunctional or polyfunctional reagents, both homo- and hetero-functional (such as those described in the catalog of the Pierce Chemical Co., Rockford, IL), may be employed as the linker group. Coupling may be effected, for example, through amino groups, carboxyl groups, sulfhydryl groups or oxidized carbohydrate residues. There are numerous references describing such methodology, e.g., U.S. Patent No. 4,671,958, to Rodwell et al.

Where a therapeutic agent is more potent when free from the antibody portion of the immunoconjugates of the present invention, it may be desirable to use a linker group which is cleavable during or upon internalization into a cell. A number of different cleavable linker groups have been described. The mechanisms for the intracellular release of an agent from these linker groups include cleavage by reduction of a disulfide bond (e.g., U.S. Patent No. 4,489,710, to Spitler), by irradiation of a photolabile bond (e.g., U.S. Patent No. 4,625,014, to Senter et al.), by hydrolysis of derivatized amino acid side chains (e.g., U.S. Patent No. 4,638,045, to Kohn et al.), by serum complement-mediated hydrolysis (e.g., U.S. Patent No. 4,671,958, to Rodwell et al.), and acid-catalyzed hydrolysis (e.g., U.S. Patent No. 4,569,789, to Blattler et al.).

It may be desirable to couple more than one agent to an antibody. In one embodiment, multiple molecules of an agent are coupled to one antibody molecule. In another embodiment, more than one type of agent may be coupled to one antibody. Regardless of the particular embodiment, immunoconjugates with more than one agent may be prepared in a variety of ways. For example, more than one agent may be coupled directly to an antibody molecule, or linkers which provide multiple sites for attachment can be used. Alternatively, a carrier can be used.

A carrier may bear the agents in a variety of ways, including covalent bonding either directly or via a linker group. Suitable carriers include proteins such as albumins (e.g., U.S. Patent No. 4,507,234, to Kato et al.), peptides and polysaccharides such as aminodextran (e.g., U.S. Patent No. 4,699,784, to Shih et al.). A carrier may also bear an agent by noncovalent bonding or by encapsulation, such as within a liposome vesicle (e.g., U.S. Patent Nos. 4,429,008 and 4,873,088). Carriers specific for radionuclide agents include radiohalogenated small molecules and chelating compounds. For example, U.S. Patent No. 4,735,792 discloses representative radiohalogenated small molecules and their synthesis. A radionuclide chelate may be formed from chelating compounds that include those containing nitrogen and sulfur atoms as the donor atoms for binding the metal, or metal oxide, radionuclide. For example, U.S. Patent No. 4,673,562, to Davison et al. discloses representative chelating compounds and their synthesis.

A variety of routes of administration for the antibodies and immunoconjugates may be used. Typically, administration will be intravenous, intramuscular, subcutaneous or in the bed of a resected tumor. It will be evident that the precise dose of the antibody/immunoconjugate will vary depending upon the antibody used, the antigen density on the tumor, and the rate of clearance of the antibody.

#### T CELLS

Immunotherapeutic compositions may also, or alternatively, comprise T cells specific for a prostate tumor protein. Such cells may generally be prepared *in vitro* or *ex vivo*, using standard procedures. For example, T cells may be isolated from bone marrow, peripheral blood, or a fraction of bone marrow or peripheral blood of a patient, using a commercially available cell separation system, such as the CEPRATE™ system, available from CellPro Inc., Bothell WA (*see also* U.S. Patent No. 5,240,856; U.S. Patent No. 5,215,926; WO 89/06280; WO 91/16116 and WO 92/07243). Alternatively, T cells may be derived from related or unrelated humans, non-human mammals, cell lines or cultures.

T cells may be stimulated with a prostate tumor polypeptide, polynucleotide encoding a prostate tumor polypeptide and/or an antigen presenting cell (APC) that expresses such a polypeptide. Such stimulation is performed under conditions and for a time sufficient to permit the generation of T cells that are specific for the polypeptide. Preferably, a prostate tumor polypeptide or polynucleotide is present within a delivery vehicle, such as a microsphere, to facilitate the generation of specific T cells.

T cells are considered to be specific for a prostate tumor polypeptide if the T cells kill target cells coated with the polypeptide or expressing a gene encoding the polypeptide. T cell specificity may be evaluated using any of a variety of standard techniques. For example, within a chromium release assay or proliferation assay, a stimulation index of more than two fold increase in lysis and/or proliferation, compared to negative controls, indicates T cell specificity. Such assays may be performed, for example, as described in Chen et al., Cancer Res. 54:1065-1070, 1994. Alternatively,

detection of the proliferation of T cells may be accomplished by a variety of known techniques. For example, T cell proliferation can be detected by measuring an increased rate of DNA synthesis (e.g., by pulse-labeling cultures of T cells with tritiated thymidine and measuring the amount of tritiated thymidine incorporated into DNA). Contact with a prostate tumor polypeptide (100 ng/ml - 100 µg/ml, preferably 200 ng/ml - 25 µg/ml) for 3 - 7 days should result in at least a two fold increase in proliferation of the T cells. Contact as described above for 2-3 hours should result in activation of the T cells, as measured using standard cytokine assays in which a two fold increase in the level of cytokine release (e.g., TNF or IFN-γ) is indicative of T cell activation (see Coligan et al., Current Protocols in Immunology, vol. 1, Wiley Interscience (Greene 1998)). T cells that have been activated in response to a prostate tumor polypeptide, polynucleotide or polypeptide-expressing APC may be CD4<sup>+</sup> and/or CD8+. Prostate tumor protein-specific T cells may be expanded using standard techniques. Within preferred embodiments, the T cells are derived from either a patient or a related, or unrelated, donor and are administered to the patient following stimulation and expansion.

For therapeutic purposes, CD4<sup>+</sup> or CD8<sup>+</sup> T cells that proliferate in response to a prostate tumor polypeptide, polynucleotide or APC can be expanded in number either *in vitro* or *in vivo*. Proliferation of such T cells *in vitro* may be accomplished in a variety of ways. For example, the T cells can be re-exposed to a prostate tumor polypeptide, or a short peptide corresponding to an immunogenic portion of such a polypeptide, with or without the addition of T cell growth factors, such as interleukin-2, and/or stimulator cells that synthesize a prostate tumor polypeptide. Alternatively, one or more T cells that proliferate in the presence of a prostate tumor protein can be expanded in number by cloning. Methods for cloning cells are well known in the art, and include limiting dilution.

### PHARMACEUTICAL COMPOSITIONS AND VACCINES

Within certain aspects, polypeptides, polynucleotides, T cells and/or binding agents disclosed herein may be incorporated into pharmaceutical compositions

or immunogenic compositions (*i.e.*, vaccines). Pharmaceutical compositions comprise one or more such compounds and a physiologically acceptable carrier. Vaccines may comprise one or more such compounds and a non-specific immune response enhancer. A non-specific immune response enhancer may be any substance that enhances an immune response to an exogenous antigen. Examples of non-specific immune response enhancers include adjuvants, biodegradable microspheres (*e.g.*, polylactic galactide) and liposomes (into which the compound is incorporated; *see e.g.*, Fullerton, U.S. Patent No. 4,235,877). Vaccine preparation is generally described in, for example, M.F. Powell and M.J. Newman, eds., "Vaccine Design (the subunit and adjuvant approach)," Plenum Press (NY, 1995). Pharmaceutical compositions and vaccines within the scope of the present invention may also contain other compounds, which may be biologically active or inactive. For example, one or more immunogenic portions of other tumor antigens may be present, either incorporated into a fusion polypeptide or as a separate compound, within the composition or vaccine.

A pharmaceutical composition or vaccine may contain DNA encoding one or more of the polypeptides as described above, such that the polypeptide is generated in situ. As noted above, the DNA may be present within any of a variety of delivery systems known to those of ordinary skill in the art, including nucleic acid expression systems, bacteria and viral expression systems. Numerous gene delivery techniques are well known in the art, such as those described by Rolland, Crit. Rev. Therap. Drug Carrier Systems 15:143-198, 1998, and references cited therein. Appropriate nucleic acid expression systems contain the necessary DNA sequences for expression in the patient (such as a suitable promoter and terminating signal). Bacterial delivery systems involve the administration of a bacterium (such as Bacillus-Calmette-Guerrin) that expresses an immunogenic portion of the polypeptide on its cell surface or secretes such an epitope. In a preferred embodiment, the DNA may be introduced using a viral expression system (e.g., vaccinia or other pox virus, retrovirus, or adenovirus), which may involve the use of a non-pathogenic (defective), replication competent virus. Suitable systems are disclosed, for example, in Fisher-Hoch et al., Proc. Natl. Acad. Sci. USA 86:317-321, 1989; Flexner et al., Ann. N.Y. Acad. Sci. 569:86-103, 1989; Flexner

et al., *Vaccine* 8:17-21, 1990; U.S. Patent Nos. 4,603,112, 4,769,330, and 5,017,487; WO 89/01973; U.S. Patent No. 4,777,127; GB 2,200,651; EP 0,345,242; WO 91/02805; Berkner, *Biotechniques* 6:616-627, 1988; Rosenfeld et al., *Science* 252:431-434, 1991; Kolls et al., *Proc. Natl. Acad. Sci. USA* 91:215-219, 1994; Kass-Eisler et al., *Proc. Natl. Acad. Sci. USA* 90:11498-11502, 1993; Guzman et al., *Circulation* 88:2838-2848, 1993; and Guzman et al., *Cir. Res.* 73:1202-1207, 1993. Techniques for incorporating DNA into such expression systems are well known to those of ordinary skill in the art. The DNA may also be "naked," as described, for example, in Ulmer et al., *Science* 259:1745-1749, 1993 and reviewed by Cohen, *Science* 259:1691-1692, 1993. The uptake of naked DNA may be increased by coating the DNA onto biodegradable beads, which are efficiently transported into the cells.

While any suitable carrier known to those of ordinary skill in the art may be employed in the pharmaceutical compositions of this invention, the type of carrier will vary depending on the mode of administration. Compositions of the present invention may be formulated for any appropriate manner of administration, including for example, topical, oral, nasal, intravenous, intracranial, intraperitoneal, subcutaneous or intramuscular administration. For parenteral administration, such as subcutaneous injection, the carrier preferably comprises water, saline, alcohol, a fat, a wax or a buffer. For oral administration, any of the above carriers or a solid carrier, such as mannitol, lactose, starch, magnesium stearate, sodium saccharine, talcum, cellulose, glucose, sucrose, and magnesium carbonate, may be employed. Biodegradable microspheres (e.g., polylactate polyglycolate) may also be employed as carriers for the pharmaceutical compositions of this invention. Suitable biodegradable microspheres are disclosed, for example, in U.S. Patent Nos. 4,897,268 and 5,075,109.

Such compositions may also comprise buffers (e.g., neutral buffered saline or phosphate buffered saline), carbohydrates (e.g., glucose, mannose, sucrose or dextrans), mannitol, proteins, polypeptides or amino acids such as glycine, antioxidants, chelating agents such as EDTA or glutathione, adjuvants (e.g., aluminum hydroxide) and/or preservatives. Alternatively, compositions of the present invention may be

formulated as a lyophilizate. Compounds may also be encapsulated within liposomes using well known technology.

Any of a variety of non-specific immune response enhancers may be employed in the vaccines of this invention. For example, an adjuvant may be included. Most adjuvants contain a substance designed to protect the antigen from rapid catabolism, such as aluminum hydroxide or mineral oil, and a stimulator of immune responses, such as lipid A, Bortadella pertussis or Mycobacterium tuberculosis derived proteins. Suitable adjuvants are commercially available as, for example, Freund's Incomplete Adjuvant and Complete Adjuvant (Difco Laboratories, Detroit, MI); Merck Adjuvant 65 (Merck and Company, Inc., Rahway, NJ); aluminum salts such as aluminum hydroxide gel (alum) or aluminum phosphate; salts of calcium, iron or zinc; an insoluble suspension of acylated tyrosine; acylated sugars; cationically or anionically derivatized polysaccharides; polyphosphazenes; biodegradable monophosphoryl lipid A and quil A. Cytokines, such as GM-CSF or interleukin-2, -7, or -12, may also be used as adjuvants.

Within the vaccines provided herein, the adjuvant composition is preferably designed to induce an immune response predominantly of the Th1 type. High levels of Th1-type cytokines (e.g., IFN-γ, IL-2 and IL-12) tend to favor the induction of cell mediated immune responses to an administered antigen. In contrast, high levels of Th2-type cytokines (e.g., IL-4, IL-5, IL-6, IL-10 and TNF-β) tend to favor the induction of humoral immune responses. Following application of a vaccine as provided herein, a patient will support an immune response that includes Th1- and Th2-type responses. Within a preferred embodiment, in which a response is predominantly Th1-type, the level of Th1-type cytokines will increase to a greater extent than the level of Th2-type cytokines. The levels of these cytokines may be readily assessed using standard assays. For a review of the families of cytokines, see Mosmann and Coffman, Ann. Rev. Immunol. 7:145-173, 1989.

Preferred adjuvants for use in eliciting a predominantly Th1-type response include, for example, a combination of monophosphoryl lipid A, preferably 3-de-O-acylated monophosphoryl lipid A (3D-MPL), together with an aluminum salt.

MPL adjuvants are available from Ribi ImmunoChem Research Inc. (Hamilton, MT; see US Patent Nos. 4,436,727; 4,877,611; 4,866,034 and 4,912,094). CpG-containing oligonucleotides (in which the CpG dinucleotide is unmethylated) also induce a predominantly Th1 response. Such oligonucleotides are well known and are described, for example, in WO 96/02555. Another preferred adjuvant is a saponin, preferably QS21, which may be used alone or in combination with other adjuvants. For example, an enhanced system involves the combination of a monophosphoryl lipid A and saponin derivative, such as the combination of QS21 and 3D-MPL as described in WO 94/00153, or a less reactogenic composition where the QS21 is quenched with cholesterol, as described in WO 96/33739. Other preferred formulations comprises an oil-in-water emulsion and tocopherol. A particularly potent adjuvant formulation involving QS21, 3D-MPL and tocopherol in an oil-in-water emulsion is described in WO 95/17210. Any vaccine provided herein may be prepared using well known methods that result in a combination of antigen, immune response enhancer and a suitable carrier or excipient.

The compositions described herein may be administered as part of a sustained release formulation (*i.e.*, a formulation such as a capsule or sponge that effects a slow release of compound following administration). Such formulations may generally be prepared using well known technology and administered by, for example, oral, rectal or subcutaneous implantation, or by implantation at the desired target site. Sustained-release formulations may contain a polypeptide, polynucleotide or antibody dispersed in a carrier matrix and/or contained within a reservoir surrounded by a rate controlling membrane. Carriers for use within such formulations are biocompatible, and may also be biodegradable; preferably the formulation provides a relatively constant level of active component release. The amount of active compound contained within a sustained release formulation depends upon the site of implantation, the rate and expected duration of release and the nature of the condition to be treated or prevented.

Any of a variety of delivery vehicles may be employed within pharmaceutical compositions and vaccines to facilitate production of an antigen-specific

immune response that targets tumor cells. Delivery vehicles include antigen presenting cells (APCs), such as dendritic cells, macrophages, B cells, monocytes and other cells that may be engineered to be efficient APCs. Such cells may, but need not, be genetically modified to increase the capacity for presenting the antigen, to improve activation and/or maintenance of the T cell response, to have anti-tumor effects *per se* and/or to be immunologically compatible with the receiver (*i.e.*, matched HLA haplotype). APCs may generally be isolated from any of a variety of biological fluids and organs, including tumor and peritumoral tissues, and may be autologous, allogeneic, syngeneic or xenogeneic cells.

Certain preferred embodiments of the present invention use dendritic cells or progenitors thereof as antigen-presenting cells. Dendritic cells are highly potent APCs (Banchereau and Steinman, *Nature 392*:245-251, 1998) and have been shown to be effective as a physiological adjuvant for eliciting prophylactic or therapeutic antitumor immunity (*see* Timmerman and Levy, *Ann. Rev. Med. 50*:507-529, 1999). In general, dendritic cells may be identified based on their typical shape (stellate *in situ*, with marked cytoplasmic processes (dendrites) visible *in vitro*) and based on the lack of differentiation markers of B cells (CD19 and CD20), T cells (CD3), monocytes (CD14) and natural killer cells (CD56), as determined using standard assays. Dendritic cells may, of course, be engineered to express specific cell-surface receptors or ligands that are not commonly found on dendritic cells *in vivo* or *ex vivo*, and such modified dendritic cells are contemplated by the present invention. As an alternative to dendritic cells, secreted vesicles antigen-loaded dendritic cells (called exosomes) may be used within a vaccine (*see* Zitvogel et al., *Nature Med. 4*:594-600, 1998).

Dendritic cells and progenitors may be obtained from peripheral blood, bone marrow, tumor-infiltrating cells, peritumoral tissues-infiltrating cells, lymph nodes, spleen, skin, umbilical cord blood or any other suitable tissue or fluid. For example, dendritic cells may be differentiated *ex vivo* by adding a combination of cytokines such as GM-CSF, IL-4, IL-13 and/or TNFα to cultures of monocytes harvested from peripheral blood. Alternatively, CD34 positive cells harvested from peripheral blood, umbilical cord blood or bone marrow may be differentiated into

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dendritic cells by adding to the culture medium combinations of GM-CSF, IL-3, TNF $\alpha$ , CD40 ligand, LPS, flt3 ligand and/or other compound(s) that induce maturation and proliferation of dendritic cells.

Dendritic cells are conveniently categorized as "immature" and "mature" cells, which allows a simple way to discriminate between two well characterized phenotypes. However, this nomenclature should not be construed to exclude all possible intermediate stages of differentiation. Immature dendritic cells are characterized as APC with a high capacity for antigen uptake and processing, which correlates with the high expression of Fcy receptor, mannose receptor and DEC-205 marker. The mature phenotype is typically characterized by a lower expression of these markers, but a high expression of cell surface molecules responsible for T cell activation such as class I and class II MHC, adhesion molecules (e.g., CD54 and CD11) and costimulatory molecules (e.g., CD40, CD80 and CD86).

APCs may generally be transfected with a polynucleotide encoding a prostate tumor protein (or portion or other variant thereof) such that the prostate tumor polypeptide, or an immunogenic portion thereof, is expressed on the cell surface. Such transfection may take place ex vivo, and a composition or vaccine comprising such transfected cells may then be used for therapeutic purposes, as described herein. Alternatively, a gene delivery vehicle that targets a dendritic or other antigen presenting cell may be administered to a patient, resulting in transfection that occurs in vivo. In vivo and ex vivo transfection of dendritic cells, for example, may generally be performed using any methods known in the art, such as those described in WO 97/24447, or the gene gun approach described by Mahvi et al., Immunology and cell Biology 75:456-460, 1997. Antigen loading of dendritic cells may be achieved by incubating dendritic cells or progenitor cells with the prostate tumor polypeptide, DNA (naked or within a plasmid vector) or RNA; or with antigen-expressing recombinant bacterium or viruses (e.g., vaccinia, fowlpox, adenovirus or lentivirus vectors). Prior to loading, the polypeptide may be covalently conjugated to an immunological partner that provides T cell help (e.g., a carrier molecule). Alternatively, a dendritic cell may be

pulsed with a non-conjugated immunological partner, separately or in the presence of the polypeptide.

#### **CANCER THERAPY**

In further aspects of the present invention, the compositions described herein may be used for immunotherapy of cancer, such as prostate cancer. Within such methods, pharmaceutical compositions and vaccines are typically administered to a patient. As used herein, a "patient" refers to any warm-blooded animal, preferably a human. A patient may or may not be afflicted with cancer. Accordingly, the above pharmaceutical compositions and vaccines may be used to prevent the development of a cancer or to treat a patient afflicted with a cancer. A cancer may be diagnosed using criteria generally accepted in the art, including the presence of a malignant tumor. Pharmaceutical compositions and vaccines may be administered either prior to or following surgical removal of primary tumors and/or treatment such as administration of radiotherapy or conventional chemotherapeutic drugs.

Within certain embodiments, immunotherapy may be active immunotherapy, in which treatment relies on the *in vivo* stimulation of the endogenous host immune system to react against tumors with the administration of immune response-modifying agents (such as polypeptides and polynucleotides disclosed herein).

Within other embodiments, immunotherapy may be passive immunotherapy, in which treatment involves the delivery of agents with established tumor-immune reactivity (such as effector cells or antibodies) that can directly or indirectly mediate antitumor effects and does not necessarily depend on an intact host immune system. Examples of effector cells include T cells as discussed above, T lymphocytes (such as CD8+ cytotoxic T lymphocytes and CD4+ T-helper tumor-infiltrating lymphocytes), killer cells (such as Natural Killer cells and lymphokine-activated killer cells), B cells and antigen-presenting cells (such as dendritic cells and macrophages) expressing a polypeptide provided herein. T cell receptors and antibody receptors specific for the polypeptides recited herein may be cloned, expressed and transferred into other vectors or effector cells for adoptive immunotherapy. The

polypeptides provided herein may also be used to generate antibodies or anti-idiotypic antibodies (as described above and in U.S. Patent No. 4,918,164) for passive immunotherapy.

Effector cells may generally be obtained in sufficient quantities for adoptive immunotherapy by growth in vitro, as described herein. Culture conditions for expanding single antigen-specific effector cells to several billion in number with retention of antigen recognition in vivo are well known in the art. Such in vitro culture conditions typically use intermittent stimulation with antigen, often in the presence of cytokines (such as IL-2) and non-dividing feeder cells. As noted above, immunoreactive polypeptides as provided herein may be used to rapidly expand antigen-specific T cell cultures in order to generate a sufficient number of cells for immunotherapy. In particular, antigen-presenting cells, such as dendritic, macrophage, monocyte, fibroblast or B cells, may be pulsed with immunoreactive polypeptides or transfected with one or more polynucleotides using standard techniques well known in the art. For example, antigen-presenting cells can be transfected with a polynucleotide having a promoter appropriate for increasing expression in a recombinant virus or other expression system. Cultured effector cells for use in therapy must be able to grow and distribute widely, and to survive long term in vivo. Studies have shown that cultured effector cells can be induced to grow in vivo and to survive long term in substantial numbers by repeated stimulation with antigen supplemented with IL-2 (see, for example, Cheever et al., Immunological Reviews 157:177, 1997).

Alternatively, a vector expressing a polypeptide recited herein may be introduced into antigen presenting cells taken from a patient and clonally propagated ex vivo for transplant back into the same patient. Transfected cells may be reintroduced into the patient using any means known in the art, preferably in sterile form by intravenous, intracavitary, intraperitoneal or intratumor administration.

Routes and frequency of administration of the therapeutic compositions disclosed herein, as well as dosage, will vary from individual to individual, and may be readily established using standard techniques. In general, the pharmaceutical compositions and vaccines may be administered by injection (e.g., intracutaneous,

intramuscular, intravenous or subcutaneous), intranasally (e.g., by aspiration) or orally. Preferably, between 1 and 10 doses may be administered over a 52 week period. Preferably, 6 doses are administered, at intervals of 1 month, and booster vaccinations may be given periodically thereafter. Alternate protocols may be appropriate for individual patients. A suitable dose is an amount of a compound that, when administered as described above, is capable of promoting an anti-tumor immune response, and is at least 10-50% above the basal (i.e., untreated) level. Such response can be monitored by measuring the anti-tumor antibodies in a patient or by vaccinedependent generation of cytolytic effector cells capable of killing the patient's tumor cells in vitro. Such vaccines should also be capable of causing an immune response that leads to an improved clinical outcome (e.g., more frequent remissions, complete or partial or longer disease-free survival) in vaccinated patients as compared to nonvaccinated patients. In general, for pharmaceutical compositions and vaccines comprising one or more polypeptides, the amount of each polypeptide present in a dose ranges from about 100 µg to 5 mg per kg of host. Suitable dose sizes will vary with the size of the patient, but will typically range from about 0.1 mL to about 5 mL.

In general, an appropriate dosage and treatment regimen provides the active compound(s) in an amount sufficient to provide therapeutic and/or prophylactic benefit. Such a response can be monitored by establishing an improved clinical outcome (e.g., more frequent remissions, complete or partial, or longer disease-free survival) in treated patients as compared to non-treated patients. Increases in preexisting immune responses to a prostate tumor protein generally correlate with an improved clinical outcome. Such immune responses may generally be evaluated using standard proliferation, cytotoxicity or cytokine assays, which may be performed using samples obtained from a patient before and after treatment.

#### METHODS FOR DETECTING CANCER

In general, a cancer may be detected in a patient based on the presence of one or more prostate tumor proteins and/or polynucleotides encoding such proteins in a biological sample (for example, blood, sera, urine and/or tumor biopsies) obtained from

the patient. In other words, such proteins may be used as markers to indicate the presence or absence of a cancer such as prostate cancer. In addition, such proteins may be useful for the detection of other cancers. The binding agents provided herein generally permit detection of the level of antigen that binds to the agent in the biological sample. Polynucleotide primers and probes may be used to detect the level of mRNA encoding a tumor protein, which is also indicative of the presence or absence of a cancer. In general, a prostate tumor sequence should be present at a level that is at least three fold higher in tumor tissue than in normal tissue

There are a variety of assay formats known to those of ordinary skill in the art for using a binding agent to detect polypeptide markers in a sample. See, e.g., Harlow and Lane, Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, 1988. In general, the presence or absence of a cancer in a patient may be determined by (a) contacting a biological sample obtained from a patient with a binding agent; (b) detecting in the sample a level of polypeptide that binds to the binding agent; and (c) comparing the level of polypeptide with a predetermined cut-off value.

In a preferred embodiment, the assay involves the use of binding agent immobilized on a solid support to bind to and remove the polypeptide from the remainder of the sample. The bound polypeptide may then be detected using a detection reagent that contains a reporter group and specifically binds to the binding agent/polypeptide complex. Such detection reagents may comprise, for example, a binding agent that specifically binds to the polypeptide or an antibody or other agent that specifically binds to the binding agent, such as an anti-immunoglobulin, protein G, protein A or a lectin. Alternatively, a competitive assay may be utilized, in which a polypeptide is labeled with a reporter group and allowed to bind to the immobilized binding agent after incubation of the binding agent with the sample. The extent to which components of the sample inhibit the binding of the labeled polypeptide to the binding agent is indicative of the reactivity of the sample with the immobilized binding agent. Suitable polypeptides for use within such assays include full length prostate tumor proteins and portions thereof to which the binding agent binds, as described above.

The solid support may be any material known to those of ordinary skill in the art to which the tumor protein may be attached. For example, the solid support may be a test well in a microtiter plate or a nitrocellulose or other suitable membrane. Alternatively, the support may be a bead or disc, such as glass, fiberglass, latex or a plastic material such as polystyrene or polyvinylchloride. The support may also be a magnetic particle or a fiber optic sensor, such as those disclosed, for example, in U.S. Patent No. 5,359,681. The binding agent may be immobilized on the solid support using a variety of techniques known to those of skill in the art, which are amply described in the patent and scientific literature. In the context of the present invention, the term "immobilization" refers to both noncovalent association, such as adsorption, and covalent attachment (which may be a direct linkage between the agent and functional groups on the support or may be a linkage by way of a cross-linking agent). Immobilization by adsorption to a well in a microtiter plate or to a membrane is preferred. In such cases, adsorption may be achieved by contacting the binding agent, in a suitable buffer, with the solid support for a suitable amount of time. The contact time varies with temperature, but is typically between about 1 hour and about 1 day. In general, contacting a well of a plastic microtiter plate (such as polystyrene or polyvinylchloride) with an amount of binding agent ranging from about 10 ng to about  $10\,\mu g$ , and preferably about  $100\,ng$  to about  $1\,\mu g$ , is sufficient to immobilize an adequate amount of binding agent.

Covalent attachment of binding agent to a solid support may generally be achieved by first reacting the support with a bifunctional reagent that will react with both the support and a functional group, such as a hydroxyl or amino group, on the binding agent. For example, the binding agent may be covalently attached to supports having an appropriate polymer coating using benzoquinone or by condensation of an aldehyde group on the support with an amine and an active hydrogen on the binding partner (see, e.g., Pierce Immunotechnology Catalog and Handbook, 1991, at A12-A13).

In certain embodiments, the assay is a two-antibody sandwich assay. This assay may be performed by first contacting an antibody that has been immobilized

on a solid support, commonly the well of a microtiter plate, with the sample, such that polypeptides within the sample are allowed to bind to the immobilized antibody. Unbound sample is then removed from the immobilized polypeptide-antibody complexes and a detection reagent (preferably a second antibody capable of binding to a different site on the polypeptide) containing a reporter group is added. The amount of detection reagent that remains bound to the solid support is then determined using a method appropriate for the specific reporter group.

More specifically, once the antibody is immobilized on the support as described above, the remaining protein binding sites on the support are typically blocked. Any suitable blocking agent known to those of ordinary skill in the art, such as bovine serum albumin or Tween 20™ (Sigma Chemical Co., St. Louis, MO). The immobilized antibody is then incubated with the sample, and polypeptide is allowed to bind to the antibody. The sample may be diluted with a suitable diluent, such as phosphate-buffered saline (PBS) prior to incubation. In general, an appropriate contact time (*i.e.*, incubation time) is a period of time that is sufficient to detect the presence of polypeptide within a sample obtained from an individual with prostate cancer. Preferably, the contact time is sufficient to achieve a level of binding that is at least about 95% of that achieved at equilibrium between bound and unbound polypeptide. Those of ordinary skill in the art will recognize that the time necessary to achieve equilibrium may be readily determined by assaying the level of binding that occurs over a period of time. At room temperature, an incubation time of about 30 minutes is generally sufficient.

Unbound sample may then be removed by washing the solid support with an appropriate buffer, such as PBS containing 0.1% Tween 20<sup>TM</sup>. The second antibody, which contains a reporter group, may then be added to the solid support. Preferred reporter groups include those groups recited above.

The detection reagent is then incubated with the immobilized antibody-polypeptide complex for an amount of time sufficient to detect the bound polypeptide. An appropriate amount of time may generally be determined by assaying the level of binding that occurs over a period of time. Unbound detection reagent is then removed

and bound detection reagent is detected using the reporter group. The method employed for detecting the reporter group depends upon the nature of the reporter group. For radioactive groups, scintillation counting or autoradiographic methods are generally appropriate. Spectroscopic methods may be used to detect dyes, luminescent groups and fluorescent groups. Biotin may be detected using avidin, coupled to a different reporter group (commonly a radioactive or fluorescent group or an enzyme). Enzyme reporter groups may generally be detected by the addition of substrate (generally for a specific period of time), followed by spectroscopic or other analysis of the reaction products.

To determine the presence or absence of a cancer, such as prostate cancer, the signal detected from the reporter group that remains bound to the solid support is generally compared to a signal that corresponds to a predetermined cut-off value. In one preferred embodiment, the cut-off value for the detection of a cancer is the average mean signal obtained when the immobilized antibody is incubated with samples from patients without the cancer. In general, a sample generating a signal that is three standard deviations above the predetermined cut-off value is considered positive for the cancer. In an alternate preferred embodiment, the cut-off value is determined using a Receiver Operator Curve, according to the method of Sackett et al., Clinical Epidemiology: A Basic Science for Clinical Medicine, Little Brown and Co., 1985, p. 106-7. Briefly, in this embodiment, the cut-off value may be determined from a plot of pairs of true positive rates (i.e., sensitivity) and false positive rates (100%-specificity) that correspond to each possible cut-off value for the diagnostic test result. The cut-off value on the plot that is the closest to the upper left-hand corner (i.e., the value that encloses the largest area) is the most accurate cut-off value, and a sample generating a signal that is higher than the cut-off value determined by this method may be considered positive. Alternatively, the cut-off value may be shifted to the left along the plot, to minimize the false positive rate, or to the right, to minimize the false negative rate. In general, a sample generating a signal that is higher than the cut-off value determined by this method is considered positive for a cancer.

In a related embodiment, the assay is performed in a flow-through or strip test format, wherein the binding agent is immobilized on a membrane, such as nitrocellulose. In the flow-through test, polypeptides within the sample bind to the immobilized binding agent as the sample passes through the membrane. A second, labeled binding agent then binds to the binding agent-polypeptide complex as a solution containing the second binding agent flows through the membrane. The detection of bound second binding agent may then be performed as described above. In the strip test format, one end of the membrane to which binding agent is bound is immersed in a solution containing the sample. The sample migrates along the membrane through a region containing second binding agent and to the area of immobilized binding agent. Concentration of second binding agent at the area of immobilized antibody indicates the presence of a cancer. Typically, the concentration of second binding agent at that site generates a pattern, such as a line, that can be read visually. The absence of such a pattern indicates a negative result. In general, the amount of binding agent immobilized on the membrane is selected to generate a visually discernible pattern when the biological sample contains a level of polypeptide that would be sufficient to generate a positive signal in the two-antibody sandwich assay, in the format discussed above. Preferred binding agents for use in such assays are antibodies and antigen-binding fragments thereof. Preferably, the amount of antibody immobilized on the membrane ranges from about 25 ng to about 1µg, and more preferably from about 50 ng to about 500 ng. Such tests can typically be performed with a very small amount of biological sample.

Of course, numerous other assay protocols exist that are suitable for use with the tumor proteins or binding agents of the present invention. The above descriptions are intended to be exemplary only. For example, it will be apparent to those of ordinary skill in the art that the above protocols may be readily modified to use prostate tumor polypeptides to detect antibodies that bind to such polypeptides in a biological sample. The detection of such prostate tumor protein specific antibodies may correlate with the presence of a cancer.

A cancer may also, or alternatively, be detected based on the presence of T cells that specifically react with a prostate tumor protein in a biological sample. Within certain methods, a biological sample comprising CD4<sup>+</sup> and/or CD8<sup>+</sup> T cells isolated from a patient is incubated with a prostate tumor polypeptide, a polynucleotide encoding such a polypeptide and/or an APC that expresses at least an immunogenic portion of such a polypeptide, and the presence or absence of specific activation of the T cells is detected. Suitable biological samples include, but are not limited to, isolated T cells. For example, T cells may be isolated from a patient by routine techniques (such as by Ficoll/Hypaque density gradient centrifugation of peripheral blood lymphocytes). T cells may be incubated in vitro for 2-9 days (typically 4 days) at 37°C with prostate tumor polypeptide (e.g., 5 - 25 µg/ml). It may be desirable to incubate another aliquot of a T cell sample in the absence of prostate tumor polypeptide to serve as a control. For CD4<sup>+</sup> T cells, activation is preferably detected by evaluating proliferation of the T cells. For CD8+ T cells, activation is preferably detected by evaluating cytolytic activity. A level of proliferation that is at least two fold greater and/or a level of cytolytic activity that is at least 20% greater than in disease-free patients indicates the presence of a cancer in the patient.

As noted above, a cancer may also, or alternatively, be detected based on the level of mRNA encoding a prostate tumor protein in a biological sample. For example, at least two oligonucleotide primers may be employed in a polymerase chain reaction (PCR) based assay to amplify a portion of a prostate tumor cDNA derived from a biological sample, wherein at least one of the oligonucleotide primers is specific for (*i.e.*, hybridizes to) a polynucleotide encoding the prostate tumor protein. The amplified cDNA is then separated and detected using techniques well known in the art, such as gel electrophoresis. Similarly, oligonucleotide probes that specifically hybridize to a polynucleotide encoding a prostate tumor protein may be used in a hybridization assay to detect the presence of polynucleotide encoding the tumor protein in a biological sample.

To permit hybridization under assay conditions, oligonucleotide primers and probes should comprise an oligonucleotide sequence that has at least about 60%,

preferably at least about 75% and more preferably at least about 90%, identity to a portion of a polynucleotide encoding a prostate tumor protein that is at least 10 nucleotides, and preferably at least 20 nucleotides, in length. Preferably, oligonucleotide primers and/or probes will hybridize to a polynucleotide encoding a polypeptide disclosed herein under moderately stringent conditions, as defined above. Oligonucleotide primers and/or probes which may be usefully employed in the diagnostic methods described herein preferably are at least 10-40 nucleotides in length. In a preferred embodiment, the oligonucleotide primers comprise at least 10 contiguous nucleotides, more preferably at least 15 contiguous nucleotides, of a DNA molecule having a sequence recited in SEQ ID NO: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375 and 381. Techniques for both PCR based assays and hybridization assays are well known in the art (see, for example, Mullis et al., Cold Spring Harbor Symp. Quant. Biol., 51:263, 1987; Erlich ed., PCR Technology, Stockton Press, NY, 1989).

One preferred assay employs RT-PCR, in which PCR is applied in conjunction with reverse transcription. Typically, RNA is extracted from a biological sample, such as biopsy tissue, and is reverse transcribed to produce cDNA molecules. PCR amplification using at least one specific primer generates a cDNA molecule, which may be separated and visualized using, for example, gel electrophoresis. Amplification may be performed on biological samples taken from a test patient and from an individual who is not afflicted with a cancer. The amplification reaction may be performed on several dilutions of cDNA spanning two orders of magnitude. A two-fold or greater increase in expression in several dilutions of the test patient sample as compared to the same dilutions of the non-cancerous sample is typically considered positive.

In another embodiment, the disclosed compositions may be used as markers for the progression of cancer. In this embodiment, assays as described above for the diagnosis of a cancer may be performed over time, and the change in the level of reactive polypeptide(s) or polynucleotide evaluated. For example, the assays may be performed every 24-72 hours for a period of 6 months to 1 year, and thereafter

performed as needed. In general, a cancer is progressing in those patients in whom the level of polypeptide or polynucleotide detected increases over time. In contrast, the cancer is not progressing when the level of reactive polypeptide or polynucleotide either remains constant or decreases with time.

Certain *in vivo* diagnostic assays may be performed directly on a tumor. One such assay involves contacting tumor cells with a binding agent. The bound binding agent may then be detected directly or indirectly via a reporter group. Such binding agents may also be used in histological applications. Alternatively, polynucleotide probes may be used within such applications.

As noted above, to improve sensitivity, multiple prostate tumor protein markers may be assayed within a given sample. It will be apparent that binding agents specific for different proteins provided herein may be combined within a single assay. Further, multiple primers or probes may be used concurrently. The selection of tumor protein markers may be based on routine experiments to determine combinations that results in optimal sensitivity. In addition, or alternatively, assays for tumor proteins provided herein may be combined with assays for other known tumor antigens.

#### DIAGNOSTIC KITS

The present invention further provides kits for use within any of the above diagnostic methods. Such kits typically comprise two or more components necessary for performing a diagnostic assay. Components may be compounds, reagents, containers and/or equipment. For example, one container within a kit may contain a monoclonal antibody or fragment thereof that specifically binds to a prostate tumor protein. Such antibodies or fragments may be provided attached to a support material, as described above. One or more additional containers may enclose elements, such as reagents or buffers, to be used in the assay. Such kits may also, or alternatively, contain a detection reagent as described above that contains a reporter group suitable for direct or indirect detection of antibody binding.

Alternatively, a kit may be designed to detect the level of mRNA encoding a prostate tumor protein in a biological sample. Such kits generally comprise

at least one oligonucleotide probe or primer, as described above, that hybridizes to a polynucleotide encoding a prostate tumor protein. Such an oligonucleotide may be used, for example, within a PCR or hybridization assay. Additional components that may be present within such kits include a second oligonucleotide and/or a diagnostic reagent or container to facilitate the detection of a polynucleotide encoding a prostate tumor protein.

The following Examples are offered by way of illustration and not by way of limitation.

#### **EXAMPLES**

#### **EXAMPLE 1**

## ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library was constructed from prostate tumor poly A+ RNA using a Superscript Plasmid System for cDNA Synthesis and Plasmid Cloning kit (BRL Life Technologies, Gaithersburg, MD 20897) following the manufacturer's protocol. Specifically, prostate tumor tissues were homogenized with polytron (Kinematica, Switzerland) and total RNA was extracted using Trizol reagent (BRL Life Technologies) as directed by the manufacturer. The poly A+ RNA was then purified using a Qiagen oligotex spin column mRNA purification kit (Qiagen, Santa Clarita, CA 91355) according to the manufacturer's protocol. First-strand cDNA was synthesized using the Notl/Oligo-dT18 primer. Double-stranded cDNA was synthesized, ligated with EcoRI/BAXI adaptors (Invitrogen, San Diego, CA) and digested with Notl. Following size fractionation with Chroma Spin-1000 columns (Clontech, Palo Alto, CA), the cDNA was ligated into the EcoRI/Notl site of pCDNA3.1 (Invitrogen) and transformed into ElectroMax *E. coli* DH10B cells (BRL Life Technologies) by electroporation.

Using the same procedure, a normal human pancreas cDNA expression library was prepared from a pool of six tissue specimens (Clontech). The cDNA libraries were characterized by determining the number of independent colonies, the percentage of clones that carried insert, the average insert size and by sequence analysis. The prostate tumor library contained 1.64 x 10<sup>7</sup> independent colonies, with 70% of clones having an insert and the average insert size being 1745 base pairs. The normal pancreas cDNA library contained 3.3 x 10<sup>6</sup> independent colonies, with 69% of clones

having inserts and the average insert size being 1120 base pairs. For both libraries, sequence analysis showed that the majority of clones had a full length cDNA sequence and were synthesized from mRNA, with minimal rRNA and mitochondrial DNA contamination.

cDNA library subtraction was performed using the above prostate tumor and normal pancreas cDNA libraries, as described by Hara *et al.* (*Blood*, *84*:189-199, 1994) with some modifications. Specifically, a prostate tumor-specific subtracted cDNA library was generated as follows. Normal pancreas cDNA library (70 μg) was digested with EcoRI, NotI, and SfuI, followed by a filling-in reaction with DNA polymerase Klenow fragment. After phenol-chloroform extraction and ethanol precipitation, the DNA was dissolved in 100 μl of H<sub>2</sub>O, heat-denatured and mixed with 100 μl (100 μg) of Photoprobe biotin (Vector Laboratories, Burlingame, CA). As recommended by the manufacturer, the resulting mixture was irradiated with a 270 W sunlamp on ice for 20 minutes. Additional Photoprobe biotin (50 μl) was added and the biotinylation reaction was repeated. After extraction with butanol five times, the DNA was ethanol-precipitated and dissolved in 23 μl H<sub>2</sub>O to form the driver DNA.

To form the tracer DNA, 10 μg prostate tumor cDNA library was digested with BamHI and XhoI, phenol chloroform extracted and passed through Chroma spin-400 columns (Clontech). Following ethanol precipitation, the tracer DNA was dissolved in 5 μl H<sub>2</sub>O. Tracer DNA was mixed with 15 μl driver DNA and 20 μl of 2 x hybridization buffer (1.5 M NaCl/10 mM EDTA/50 mM HEPES pH 7.5/0.2% sodium dodecyl sulfate), overlaid with mineral oil, and heat-denatured completely. The sample was immediately transferred into a 68 °C water bath and incubated for 20 hours (long hybridization [LH]). The reaction mixture was then subjected to a streptavidin treatment followed by phenol/chloroform extraction. This process was repeated three more times. Subtracted DNA was precipitated, dissolved in 12 μl H<sub>2</sub>O, mixed with 8 μl driver DNA and 20 μl of 2 x hybridization buffer, and subjected to a hybridization at 68 °C for 2 hours (short hybridization [SH]). After removal of biotinylated double-stranded DNA, subtracted cDNA was ligated into BamHI/XhoI site of chloramphenicol resistant pBCSK<sup>+</sup> (Stratagene, La Jolla, CA 92037) and transformed into ElectroMax E.

coli DH10B cells by electroporation to generate a prostate tumor specific subtracted cDNA library (referred to as "prostate subtraction 1").

To analyze the subtracted cDNA library, plasmid DNA was prepared from 100 independent clones, randomly picked from the subtracted prostate tumor specific library and grouped based on insert size. Representative cDNA clones were further characterized by DNA sequencing with a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A (Foster City, CA). Six cDNA clones, hereinafter referred to as F1-13, F1-12, F1-16, H1-1, H1-9 and H1-4, were shown to be abundant in the subtracted prostate-specific cDNA library. The determined 3' and 5' cDNA sequences for F1-12 are provided in SEQ ID NO: 2 and 3, respectively, with determined 3' cDNA sequences for F1-13, F1-16, H1-1, H1-9 and H1-4 being provided in SEQ ID NO: 1 and 4-7, respectively.

The cDNA sequences for the isolated clones were compared to known sequences in the gene bank using the EMBL and GenBank databases (release 96). Four of the prostate tumor cDNA clones, F1-13, F1-16, H1-1, and H1-4, were determined to encode the following previously identified proteins: prostate specific antigen (PSA), human glandular kallikrein, human tumor expression enhanced gene, and mitochondria cytochrome C oxidase subunit II. H1-9 was found to be identical to a previously identified human autonomously replicating sequence. No significant homologies to the cDNA sequence for F1-12 were found.

Subsequent studies led to the isolation of a full-length cDNA sequence for F1-12. This sequence is provided in SEQ ID NO: 107, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 108.

To clone less abundant prostate tumor specific genes, cDNA library subtraction was performed by subtracting the prostate tumor cDNA library described above with the normal pancreas cDNA library and with the three most abundant genes in the previously subtracted prostate tumor specific cDNA library: human glandular kallikrein, prostate specific antigen (PSA), and mitochondria cytochrome C oxidase subunit II. Specifically, 1 µg each of human glandular kallikrein, PSA and mitochondria cytochrome C oxidase subunit II cDNAs in pCDNA3.1 were added to the

driver DNA and subtraction was performed as described above to provide a second subtracted cDNA library hereinafter referred to as the "subtracted prostate tumor specific cDNA library with spike".

Twenty-two cDNA clones were isolated from the subtracted prostate tumor specific cDNA library with spike. The determined 3' and 5' cDNA sequences for the clones referred to as J1-17, L1-12, N1-1862, J1-13, J1-19, J1-25, J1-24, K1-58, K1-63, L1-4 and L1-14 are provided in SEQ ID NOS: 8-9, 10-11, 12-13, 14-15, 16-17, 18-19, 20-21, 22-23, 24-25, 26-27 and 28-29, respectively. The determined 3' cDNA sequences for the clones referred to as J1-12, J1-16, J1-21, K1-48, K1-55, L1-2, L1-6, N1-1858, N1-1860, N1-1861, N1-1864 are provided in SEQ ID NOS: 30-40, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to three of the five most abundant DNA species, (J1-17, L1-12 and N1-1862; SEQ ID NOS: 8-9, 10-11 and 12-13, respectively). Of the remaining two most abundant species, one (J1-12; SEQ ID NO:30) was found to be identical to the previously identified human pulmonary surfactant-associated protein, and the other (K1-48; SEQ ID NO:33) was determined to have some homology to R. norvegicus mRNA for 2-arylpropionyl-CoA epimerase. Of the 17 less abundant cDNA clones isolated from the subtracted prostate tumor specific cDNA library with spike, four (J1-16, K1-55, L1-6 and N1-1864; SEQ ID NOS:31, 34, 36 and 40, respectively) were found to be identical to previously identified sequences, two (J1-21 and N1-1860; SEQ ID NOS: 32 and 38, respectively) were found to show some homology to nonhuman sequences, and two (L1-2 and N1-1861; SEQ ID NOS: 35 and 39, respectively) were found to show some homology to known human sequences. No significant homologies were found to the polypeptides J1-13, J1-19, J1-24, J1-25, K1-58, K1-63, L1-4, L1-14 (SEQ ID NOS: 14-15, 16-17, 20-21, 18-19, 22-23, 24-25, 26-27, 28-29, respectively).

Subsequent studies led to the isolation of full length cDNA sequences for J1-17, L1-12 and N1-1862 (SEQ ID NOS: 109-111, respectively). The corresponding predicted amino acid sequences are provided in SEQ ID NOS: 112-114. L1-12 is also referred to as P501S.

In a further experiment, four additional clones were identified by subtracting a prostate tumor cDNA library with normal prostate cDNA prepared from a pool of three normal prostate poly A+ RNA (referred to as "prostate subtraction 2"). The determined cDNA sequences for these clones, hereinafter referred to as U1-3064, U1-3065, V1-3692 and 1A-3905, are provided in SEQ ID NO: 69-72, respectively. Comparison of the determined sequences with those in the gene bank revealed no significant homologies to U1-3065.

A second subtraction with spike (referred to as "prostate subtraction spike 2") was performed by subtracting a prostate tumor specific cDNA library with spike with normal pancreas cDNA library and further spiked with PSA, J1-17, pulmonary surfactant-associated protein, mitochondrial DNA, cytochrome c oxidase subunit II, N1-1862, autonomously replicating sequence, L1-12 and tumor expression enhanced gene. Four additional clones, hereinafter referred to as V1-3686, R1-2330, 1B-3976 and V1-3679, were isolated. The determined cDNA sequences for these clones are provided in SEQ ID NO:73-76, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to V1-3686 and R1-2330.

Further analysis of the three prostate subtractions described above (prostate subtraction 2, subtracted prostate tumor specific cDNA library with spike, and prostate subtraction spike 2) resulted in the identification of sixteen additional clones, referred to as 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1G-4734, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4810, 1I-4811, 1J-4876, 1K-4884 and 1K-4896. The determined cDNA sequences for these clones are provided in SEQ ID NOS: 77-92, respectively. Comparison of these sequences with those in the gene bank as described above, revealed no significant homologies to 1G-4741, 1G-4734, 1I-4807, 1J-4876 and 1K-4896 (SEQ ID NOS: 79, 81, 87, 90 and 92, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4736, 1G-4738, 1G-4741, 1G-4744, 1H-4774, 1H-4781, 1H-4785, 1H-4787, 1H-4796, 1I-4807, 1J-4876, 1K-4884 and 1K-4896, provided in SEQ ID NOS: 179-188 and 191-193,

respectively, and to the determination of additional partial cDNA sequences for 1I-4810 and 1I-4811, provided in SEQ ID NOS: 189 and 190, respectively.

Additional studies with prostate subtraction spike 2 resulted in the isolation of three more clones. Their sequences were determined as described above and compared to the most recent GenBank. All three clones were found to have homology to known genes, which are Cysteine-rich protein, KIAA0242, and KIAA0280 (SEQ ID NO: 317, 319, and 320, respectively). Further analysis of these clones by Synteni microarray (Synteni, Palo Alto, CA) demonstrated that all three clones were over-expressed in most prostate tumors and prostate BPH, as well as in the majority of normal prostate tissues tested, but low expression in all other normal tissues.

An additional subtraction was performed by subtracting a normal prostate cDNA library with normal pancreas cDNA (referred to as "prostate subtraction 3"). This led to the identification of six additional clones referred to as 1G-4761, 1G-4762, 1H-4766, 1H-4770, 1H-4771 and 1H-4772 (SEQ ID NOS: 93-98). Comparison of these sequences with those in the gene bank revealed no significant homologies to 1G-4761 and 1H-4771 (SEQ ID NOS: 93 and 97, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1G-4761, 1G-4762, 1H-4766 and 1H-4772 provided in SEQ ID NOS: 194-196 and 199, respectively, and to the determination of additional partial cDNA sequences for 1H-4770 and 1H-4771, provided in SEQ ID NOS: 197 and 198, respectively.

Subtraction of a prostate tumor cDNA library, prepared from a pool of polyA+ RNA from three prostate cancer patients, with a normal pancreas cDNA library (prostate subtraction 4) led to the identification of eight clones, referred to as 1D-4297, 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280 (SEQ ID NOS: 99-107). These sequences were compared to those in the gene bank as described above. No significant homologies were found to 1D-4283 and 1D-4304 (SEQ ID NOS: 103 and 104, respectively). Further analysis of the isolated clones led to the determination of extended cDNA sequences for 1D-4309, 1D.1-4278, 1D-4288, 1D-4283, 1D-4304, 1D-4296 and 1D-4280, provided in SEQ ID NOS: 200-206, respectively.

cDNA clones isolated in prostate subtraction 1 and prostate subtraction 2, described above, were colony PCR amplified and their mRNA expression levels in prostate tumor, normal prostate and in various other normal tissues were determined using microarray technology (Synteni, Palo Alto, CA). Briefly, the PCR amplification products were dotted onto slides in an array format, with each product occupying a unique location in the array. mRNA was extracted from the tissue sample to be tested, reverse transcribed, and fluorescent-labeled cDNA probes were generated. microarrays were probed with the labeled cDNA probes, the slides scanned and fluorescence intensity was measured. This intensity correlates with the hybridization intensity. Two clones (referred to as P509S and P510S) were found to be overexpressed in prostate tumor and normal prostate and expressed at low levels in all other normal tissues tested (liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon). The determined cDNA sequences for P509S and P510S are provided in SEQ ID NO: 223 and 224, respectively. Comparison of these sequences with those in the gene bank as described above, revealed some homology to previously identified ESTs.

Additional, studies led to the isolation of the full-length cDNA sequence for P509S. This sequence is provided in SEQ ID NO: 332, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 339.

### EXAMPLE 2

# DETERMINATION OF TISSUE SPECIFICITY OF PROSTATE TUMOR POLYPEPTIDES

Using gene specific primers, mRNA expression levels for the representative prostate tumor polypeptides F1-16, H1-1, J1-17 (also referred to as P502S), L1-12 (also referred to as P501S), F1-12 (also referred to as P504S) and N1-1862 (also referred to as P503S) were examined in a variety of normal and tumor tissues using RT-PCR.

Briefly, total RNA was extracted from a variety of normal and tumor tissues using Trizol reagent as described above. First strand synthesis was carried out using 1-2  $\mu g$  of total RNA with SuperScript II reverse transcriptase (BRL Life Technologies) at 42  $^{\circ}C$  for one hour. The cDNA was then amplified by PCR with genespecific primers. To ensure the semi-quantitative nature of the RT-PCR,  $\beta$ -actin was used as an internal control for each of the tissues examined. First, serial dilutions of the first strand cDNAs were prepared and RT-PCR assays were performed using  $\beta$ -actin specific primers. A dilution was then chosen that enabled the linear range amplification of the  $\beta$ -actin template and which was sensitive enough to reflect the differences in the initial copy numbers. Using these conditions, the  $\beta$ -actin levels were determined for each reverse transcription reaction from each tissue. DNA contamination was minimized by DNase treatment and by assuring a negative PCR result when using first strand cDNA that was prepared without adding reverse transcriptase.

mRNA Expression levels were examined in four different types of tumor tissue (prostate tumor from 2 patients, breast tumor from 3 patients, colon tumor, lung tumor), and sixteen different normal tissues, including prostate, colon, kidney, liver, lung, ovary, pancreas, skeletal muscle, skin, stomach, testes, bone marrow and brain. F1-16 was found to be expressed at high levels in prostate tumor tissue, colon tumor and normal prostate, and at lower levels in normal liver, skin and testes, with expression being undetectable in the other tissues examined. H1-1 was found to be expressed at high levels in prostate tumor, lung tumor, breast tumor, normal prostate, normal colon and normal brain, at much lower levels in normal lung, pancreas, skeletal muscle, skin, small intestine, bone marrow, and was not detected in the other tissues tested. J1-17 (P502S) and L1-12 (P501S) appear to be specifically over-expressed in prostate, with both genes being expressed at high levels in prostate tumor and normal prostate but at low to undetectable levels in all the other tissues examined. N1-1862 (P503S) was found to be over-expressed in 60% of prostate tumors and detectable in normal colon and kidney. The RT-PCR results thus indicate that F1-16, H1-1, J1-17 (P502S), N1-1862 (P503S) and L1-12 (P501S) are either prostate specific or are expressed at significantly elevated levels in prostate.

Further RT-PCR studies showed that F1-12 (P504S) is over-expressed in 60% of prostate tumors, detectable in normal kidney but not detectable in all other tissues tested. Similarly, R1-2330 was shown to be over-expressed in 40% of prostate tumors, detectable in normal kidney and liver, but not detectable in all other tissues tested. U1-3064 was found to be over-expressed in 60% of prostate tumors, and also expressed in breast and colon tumors, but was not detectable in normal tissues.

RT-PCR characterization of R1-2330, U1-3064 and 1D-4279 showed that these three antigens are over-expressed in prostate and/or prostate tumors.

Northern analysis with four prostate tumors, two normal prostate samples, two BPH prostates, and normal colon, kidney, liver, lung, pancrease, skeletal muscle, brain, stomach, testes, small intestine and bone marrow, showed that L1-12 (P501S) is over-expressed in prostate tumors and normal prostate, while being undetectable in other normal tissues tested. J1-17 (P502S) was detected in two prostate tumors and not in the other tissues tested. N1-1862 (P503S) was found to be over-expressed in three prostate tumors and to be expressed in normal prostate, colon and kidney, but not in other tissues tested. F1-12 (P504S) was found to be highly expressed in two prostate tumors and to be undetectable in all other tissues tested.

The microarray technology described above was used to determine the expression levels of representative antigens described herein in prostate tumor, breast tumor and the following normal tissues: prostate, liver, pancreas, skin, bone marrow, brain, breast, adrenal gland, bladder, testes, salivary gland, large intestine, kidney, ovary, lung, spinal cord, skeletal muscle and colon. L1-12 (P501S) was found to be over-expressed in normal prostate and prostate tumor, with some expression being detected in normal skeletal muscle. Both J1-12 and F1-12 (P504S) were found to be over-expressed in prostate tumor, with expression being lower or undetectable in all other tissues tested. N1-1862 (P503S) was found to be expressed at high levels in prostate tumor and normal prostate, and at low levels in normal large intestine and normal colon, with expression being undetectable in all other tissues tested. R1-2330 was found to be over-expressed in prostate tumor and normal prostate, and to be expressed at lower levels in all other tissues tested. 1D-4279 was found to be over-

expressed in prostate tumor and normal prostate, expressed at lower levels in normal spinal cord, and to be undetectable in all other tissues tested.

Further microarray analysis to specifically address the extent to which P501S (SEQ ID NO: 110) was expressed in breast tumor revealed moderate over-expression not only in breast tumor, but also in metastatic breast tumor (2/31), with negligible to low expression in normal tissues. This data suggests that P501S may be over-expressed in various breast tumors as well as in prostate tumors.

The expression levels of 32 ESTs (expressed sequence tags) described by Vasmatzis *et al.* (*Proc. Natl. Acad. Sci. USA 95*:300-304, 1998) in a variety of tumor and normal tissues were examined by microarray technology as described above. Two of these clones (referred to as P1000C and P1001C) were found to be over-expressed in prostate tumor and normal prostate, and expressed at low to undetectable levels in all other tissues tested (normal aorta, thymus, resting and activated PBMC, epithelial cells, spinal cord, adrenal gland, fetal tissues, skin, salivary gland, large intestine, bone marrow, liver, lung, dendritic cells, stomach, lymph nodes, brain, heart, small intestine, skeletal muscle, colon and kidney. The determined cDNA sequences for P1000C and P1001C are provided in SEQ ID NO: 384 and 472, respectively. The sequence of P1001C was found to show some homology to the previously isolated Human mRNA for JM27 protein. No significant homologies were found to the sequence of P1000C.

The expression of the polypeptide encoded by the full length cDNA sequence for F1-12 (also referred to as P504S; SEQ ID NO: 108) was investigated by immunohistochemical analysis. Rabbit-anti-P504S polyclonal antibodies were generated against the full length P504S protein by standard techniques. Subsequent isolation and characterization of the polyclonal antibodies were also performed by techniques well known in the art. Immunohistochemical analysis showed that the P504S polypeptide was expressed in 100% of prostate carcinoma samples tested (n=5).

The rabbit-anti-P504S polyclonal antibody did not appear to label benign prostate cells with the same cytoplasmic granular staining, but rather with light nuclear staining. Analysis of normal tissues revealed that the encoded polypeptide was found to be expressed in some, but not all normal human tissues. Positive

cytoplasmic staining with rabbit-anti-P504S polyclonal antibody was found in normal human kidney, liver, brain, colon and lung-associated macrophages, whereas heart and bone marrow were negative.

This data indicates that the P504S polypeptide is present in prostate cancer tissues, and that there are qualitative and quantitative differences in the staining between benign prostatic hyperplasia tissues and prostate cancer tissues, suggesting that this polypeptide may be detected selectively in prostate tumors and therefore be useful in the diagnosis of prostate cancer.

## EXAMPLE 3 ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA subtraction library, containing cDNA from normal prostate subtracted with ten other normal tissue cDNAs (brain, heart, kidney, liver, lung, ovary, placenta, skeletal muscle, spleen and thymus) and then submitted to a first round of PCR amplification, was purchased from Clontech. This library was subjected to a second round of PCR amplification, following the manufacturer's protocol. The resulting cDNA fragments were subcloned into the vector pT7 Blue T-vector (Novagen, Madison, WI) and transformed into XL-1 Blue MRF' *E. coli* (Stratagene). DNA was isolated from independent clones and sequenced using a Perkin Elmer/Applied Biosystems Division Automated Sequencer Model 373A.

Fifty-nine positive clones were sequenced. Comparison of the DNA sequences of these clones with those in the gene bank, as described above, revealed no significant homologies to 25 of these clones, hereinafter referred to as P5, P8, P9, P18, P20, P30, P34, P36, P38, P39, P42, P49, P50, P53, P55, P60, P64, P65, P73, P75, P76, P79 and P84. The determined cDNA sequences for these clones are provided in SEQ ID NO: 41-45, 47-52 and 54-65, respectively. P29, P47, P68, P80 and P82 (SEQ ID NO: 46, 53 and 66-68, respectively) were found to show some degree of homology to

previously identified DNA sequences. To the best of the inventors' knowledge, none of these sequences have been previously shown to be present in prostate.

Further studies using the PCR-based methodology described above resulted in the isolation of more than 180 additional clones, of which 23 clones were found to show no significant homologies to known sequences. The determined cDNA sequences for these clones are provided in SEQ ID NO: 115-123, 127, 131, 137, 145, 147-151, 153, 156-158 and 160. Twenty-three clones (SEQ ID NO: 124-126, 128-130, 132-136, 138-144, 146, 152, 154, 155 and 159) were found to show some homology to previously identified ESTs. An additional ten clones (SEQ ID NO: 161-170) were found to have some degree of homology to known genes. Larger cDNA clones containing the P20 sequence represent splice variants of a gene referred to as P703P. The determined DNA sequence for the variants referred to as DE1, DE13 and DE14 are provided in SEQ ID NOS: 171, 175 and 177, respectively, with the corresponding predicted amino acid sequences being provided in SEQ ID NO: 172, 176 and 178, respectively. The determined cDNA sequence for an extended spliced form of P703 is provided in SEQ ID NO: 225. The DNA sequences for the splice variants referred to as DE2 and DE6 are provided in SEQ ID NOS: 173 and 174, respectively.

mRNA Expression levels for representative clones in tumor tissues (prostate (n=5), breast (n=2), colon and lung) normal tissues (prostate (n=5), colon, kidney, liver, lung (n=2), ovary (n=2), skeletal muscle, skin, stomach, small intestine and brain), and activated and non-activated PBMC was determined by RT-PCR as described above. Expression was examined in one sample of each tissue type unless otherwise indicated.

P9 was found to be highly expressed in normal prostate and prostate tumor compared to all normal tissues tested except for normal colon which showed comparable expression. P20, a portion of the P703P gene, was found to be highly expressed in normal prostate and prostate tumor, compared to all twelve normal tissues tested. A modest increase in expression of P20 in breast tumor (n=2), colon tumor and lung tumor was seen compared to all normal tissues except lung (1 of 2). Increased expression of P18 was found in normal prostate, prostate tumor and breast tumor

compared to other normal tissues except lung and stomach. A modest increase in expression of P5 was observed in normal prostate compared to most other normal tissues. However, some elevated expression was seen in normal lung and PBMC. Elevated expression of P5 was also observed in prostate tumors (2 of 5), breast tumor and one lung tumor sample. For P30, similar expression levels were seen in normal prostate and prostate tumor, compared to six of twelve other normal tissues tested. Increased expression was seen in breast tumors, one lung tumor sample and one colon tumor sample, and also in normal PBMC. P29 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to the majority of normal tissues. However, substantial expression of P29 was observed in normal colon and normal lung (2 of 2). P80 was found to be over-expressed in prostate tumor (5 of 5) and normal prostate (5 of 5) compared to all other normal tissues tested, with increased expression also being seen in colon tumor.

Further studies resulted in the isolation of twelve additional clones, hereinafter referred to as 10-d8, 10-h10, 11-c8, 7-g6, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3, 8-h11, 9-f12 and 9-f3. The determined DNA sequences for 10-d8, 10-h10, 11-c8, 8-d4, 8-d9, 8-h11, 9-f12 and 9-f3 are provided in SEQ ID NO: 207, 208, 209, 216, 217, 220, 221 and 222, respectively. The determined forward and reverse DNA sequences for 7-g6, 8-b5, 8-b6 and 8-g3 are provided in SEQ ID NO: 210 and 211; 212 and 213; 214 and 215; and 218 and 219, respectively. Comparison of these sequences with those in the gene bank revealed no significant homologies to the sequence of 9-f3. The clones 10-d8, 11-c8 and 8-h11 were found to show some homology to previously isolated ESTs, while 10-h10, 8-b5, 8-b6, 8-d4, 8-d9, 8-g3 and 9-f12 were found to show some homology to previously identified genes. Further characterization of 7-G6 and 8-G3 showed identity to the known genes PAP and PSA, respectively.

mRNA expression levels for these clones were determined using the micro-array technology described above. The clones 7-G6, 8-G3, 8-B5, 8-B6, 8-D4, 8-D9, 9-F3, 9-F12, 9-H3, 10-A2, 10-A4, 11-C9 and 11-F2 were found to be over-expressed in prostate tumor and normal prostate, with expression in other tissues tested being low or undetectable. Increased expression of 8-F11 was seen in prostate tumor

and normal prostate, bladder, skeletal muscle and colon. Increased expression of 10-H10 was seen in prostate tumor and normal prostate, bladder, lung, colon, brain and large intestine. Increased expression of 9-B1 was seen in prostate tumor, breast tumor, and normal prostate, salivary gland, large intestine and skin, with increased expression of 11-C8 being seen in prostate tumor, and normal prostate and large intestine.

An additional cDNA fragment derived from the PCR-based normal prostate subtraction, described above, was found to be prostate specific by both micro-array technology and RT-PCR. The determined cDNA sequence of this clone (referred to as 9-A11) is provided in SEQ ID NO: 226. Comparison of this sequence with those in the public databases revealed 99% identity to the known gene HOXB13.

Further studies led to the isolation of the clones 8-C6 and 8-H7. The determined cDNA sequences for these clones are provided in SEQ ID NO: 227 and 228, respectively. These sequences were found to show some homology to previously isolated ESTs.

PCR and hybridization-based methodologies were employed to obtain longer cDNA sequences for clone P20 (also referred to as P703P), yielding three additional cDNA fragments that progressively extend the 5' end of the gene. These fragments, referred to as P703PDE5, P703P6.26, and P703PX-23 (SEQ ID NO: 326, 328 and 330, with the predicted corresponding amino acid sequences being provided in SEQ ID NO: 327, 329 and 331, respectively) contain additional 5' sequence. P703PDE5 was recovered by screening of a cDNA library (#141-26) with a portion of P703P as a probe. P703P6.26 was recovered from a mixture of three prostate tumor cDNAs and P703PX\_23 was recovered from cDNA library (#438-48). Together, the additional sequences include all of the putative mature serine protease along with part of the putative signal sequence. Further studies using a PCR-based subtraction library of a prostate tumor pool subtracted against a pool of normal tissues (referred to as JP: PCR subtraction) resulted in the isolation of thirteen additional clones, seven of which did not share any significant homology to known GenBank sequences. The determined cDNA sequences for these seven clones (P711P, P712P, novel 23, P774P, P775P, P710P and P768P) are provided in SEQ ID NO: 307-311, 313 and 315, respectively.

The remaining six clones (SEQ ID NO: 316 and 321-325) were shown to share some homology to known genes. By microarray analysis, all thirteen clones showed three or more fold over-expression in prostate tissues, including prostate tumors, BPH and normal prostate as compared to normal non-prostate tissues. Clones P711P, P712P, novel 23 and P768P showed over-expression in most prostate tumors and BPH tissues tested (n=29), and in the majority of normal prostate tissues (n=4), but background to low expression levels in all normal tissues. Clones P774P, P775P and P710P showed comparatively lower expression and expression in fewer prostate tumors and BPH samples, with negative to low expression in normal prostate.

The full-length cDNA for P711P was obtained by employing the partial sequence of SEQ ID NO: 307 to screen a prostate cDNA library. Specifically, a directionally cloned prostate cDNA library was prepared using standard techniques. One million colonies of this library were plated onto LB/Amp plates. Nylon membrane filters were used to lift these colonies, and the cDNAs which were picked up by these filters were denatured and cross-linked to the filters by UV light. The P711P cDNA fragment of SEQ ID NO: 307 was radio-labeled and used to hybridize with these filters. Positive clones were selected, and cDNAs were prepared and sequenced using an automatic Perkin Elmer/Applied Biosystems sequencer. The determined full-length sequence of P711P is provided in SEQ ID NO: 382, with the corresponding predicted amino acid sequence being provided in SEQ ID NO: 383.

Using PCR and hybridization-based methodologies, additional cDNA sequence information was derived for two clones described above, 11-C9 and 9-F3, herein after referred to as P707P and P714P, respectively (SEQ ID NO: 333 and 334). After comparison with the most recent GenBank, P707P was found to be a splice variant of the known gene HoxB13. In contrast, no significant homologies to P714P were found.

Clones 8-B3, P89, P98, P130 and P201 (as disclosed in U.S. Patent Application No. 09/020,956, filed February 9, 1998) were found to be contained within one contiguous sequence, referred to as P705P (SEQ ID NO: 335, with the predicted

amino acid sequence provided in SEQ ID NO: 336), which was determined to be a splice variant of the known gene NKX 3.1.

### EXAMPLE 4 SYNTHESIS OF POLYPEPTIDES

Polypeptides may be synthesized on a Perkin Elmer/Applied Biosystems 430A peptide synthesizer using FMOC chemistry with HPTU (O-Benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate) activation. A Gly-Cys-Gly sequence may be attached to the amino terminus of the peptide to provide a method of conjugation, binding to an immobilized surface, or labeling of the peptide. Cleavage of the peptides from the solid support may be carried out using the following cleavage mixture: trifluoroacetic acid:ethanedithiol:thioanisole:water:phenol (40:1:2:2:3). After cleaving for 2 hours, the peptides may be precipitated in cold methyl-t-butyl-ether. The peptide pellets may then be dissolved in water containing 0.1% trifluoroacetic acid (TFA) and lyophilized prior to purification by C18 reverse phase HPLC. A gradient of 0%-60% acetonitrile (containing 0.1% TFA) in water (containing 0.1% TFA) may be used to elute the peptides. Following lyophilization of the pure fractions, the peptides may be characterized using electrospray or other types of mass spectrometry and by amino acid analysis.

### **EXAMPLE 5**

## FURTHER ISOLATION AND CHARACTERIZATION OF PROSTATE TUMOR POLYPEPTIDES BY PCR-BASED SUBTRACTION

A cDNA library generated from prostate primary tumor mRNA as described above was subtracted with cDNA from normal prostate. The subtraction was performed using a PCR-based protocol (Clontech), which was modified to generate larger fragments. Within this protocol, tester and driver double stranded cDNA were

separately digested with five restriction enzymes that recognize six-nucleotide restriction sites (MluI, MscI, PvuII, SalI and StuI). This digestion resulted in an average cDNA size of 600 bp, rather than the average size of 300 bp that results from digestion with Rsal according to the Clontech protocol. This modification did not affect the subtraction efficiency. Two tester populations were then created with different adapters, and the driver library remained without adapters.

The tester and driver libraries were then hybridized using excess driver cDNA. In the first hybridization step, driver was separately hybridized with each of the two tester cDNA populations. This resulted in populations of (a) unhybridized tester cDNAs, (b) tester cDNAs hybridized to other tester cDNAs, (c) tester cDNAs hybridized to driver cDNAs and (d) unhybridized driver cDNAs. The two separate hybridization reactions were then combined, and rehybridized in the presence of additional denatured driver cDNA. Following this second hybridization, in addition to populations (a) through (d), a fifth population (e) was generated in which tester cDNA with one adapter hybridized to tester cDNA with the second adapter. Accordingly, the second hybridization step resulted in enrichment of differentially expressed sequences which could be used as templates for PCR amplification with adaptor-specific primers.

The ends were then filled in, and PCR amplification was performed using adaptor-specific primers. Only population (e), which contained tester cDNA that did not hybridize to driver cDNA, was amplified exponentially. A second PCR amplification step was then performed, to reduce background and further enrich differentially expressed sequences.

This PCR-based subtraction technique normalizes differentially expressed cDNAs so that rare transcripts that are overexpressed in prostate tumor tissue may be recoverable. Such transcripts would be difficult to recover by traditional subtraction methods.

In addition to genes known to be overexpressed in prostate tumor, seventy-seven further clones were identified. Sequences of these partial cDNAs are provided in SEQ ID NO: 29 to 305. Most of these clones had no significant homology to database sequences. Exceptions were JPTPN23 (SEQ ID NO: 231; similarity to pig

valosin-containing protein), JPTPN30 (SEQ ID NO: 234; similarity to rat mRNA for proteasome subunit), JPTPN45 (SEQ ID NO: 243; similarity to rat *norvegicus* cytosolic NADP-dependent isocitrate dehydrogenase), JPTPN46 (SEQ ID NO: 244; similarity to human subclone H8 4 d4 DNA sequence), JP1D6 (SEQ ID NO: 265; similarity to *G. gallus* dynein light chain-A), JP8D6 (SEQ ID NO: 288; similarity to human BAC clone RG016J04), JP8F5 (SEQ ID NO: 289; similarity to human subclone H8 3 b5 DNA sequence), and JP8E9 (SEQ ID NO: 299; similarity to human Alu sequence).

Additional studies using the PCR-based subtraction library consisting of a prostate tumor pool subtracted against a normal prostate pool (referred to as PT-PN PCR subtraction) yielded three additional clones. Comparison of the cDNA sequences of these clones with the most recent release of GenBank revealed no significant homologies to the two clones referred to as P715P and P767P (SEQ ID NO: 312 and 314). The remaining clone was found to show some homology to the known gene KIAA0056 (SEQ ID NO: 318). Using microarray analysis to measure mRNA expression levels in various tissues, all three clones were found to be over-expressed in prostate tumors and BPH tissues. Specifically, clone P715P was over-expressed in most prostate tumors and BPH tissues by a factor of three or greater, with elevated expression seen in the majority of normal prostate samples and in fetal tissue, but negative to low expression in all other normal tissues. Clone P767P was over-expressed in several prostate tumors and BPH tissues, with moderate expression levels in half of the normal prostate samples, and background to low expression in all other normal tissues tested.

Further analysis, by microarray as described above, of the PT-PN PCR subtraction library and of a DNA subtraction library containing cDNA from prostate tumor subtracted with a pool of normal tissue cDNAs, led to the isolation of 27 additional clones (SEQ ID NO: 340-365 and 381) which were determined to be overexpressed in prostate tumor. The clones of SEQ ID NO: 341, 342, 345, 347, 348, 349, 351, 355-359, 361, 362 and 364 were also found to be expressed in normal prostate. Expression of all 26 clones in a variety of normal tissues was found to be low or undetectable, with the exception of P544S (SEQ ID NO: 356) which was found to be

expressed in small intestine. Of the 26 clones, 10 (SEQ ID NO: 340-349) were found to show some homology to previously identified sequences. No significant homologies were found to the clones of SEQ ID NO: 350-365.

## EXAMPLE 6 . PEPTIDE PRIMING OF MICE AND PROPAGATION OF CTL LINES

6.1. This Example illustrates the preparation of a CTL cell line specific for cells expressing the P502S gene.

Mice expressing the transgene for human HLA A2.1 (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with P2S#12 peptide (VLGWVAEL; SEQ ID NO: 306), which is derived from the P502S gene (also referred to herein as J1-17, SEQ ID NO: 8), as described by Theobald et al., Proc. Natl. Acad Sci. USA 92:11993-11997, 1995 with the following modifications. Mice were immunized with 100µg of P2S#12 and 120µg of an I-Ab binding peptide derived from hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and using a nylon mesh single cell suspensions prepared. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (RPMI-1640; Gibco BRL, Gaithersburg, MD) containing 10% FCS, 2mM Glutamine (Gibco BRL), sodium pyruvate (Gibco BRL), non-essential amino acids (Gibco BRL), 2 x 10<sup>-5</sup> M 2mercaptoethanol, 50U/ml penicillin and streptomycin, and cultured in the presence of irradiated (3000 rads) P2S#12-pulsed (5mg/ml P2S#12 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7µg/ml dextran sulfate and 25µg/ml LPS for 3 days). Six days later, cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 106/ml peptide pulsed irradiated (20,000 rads) EL4A2Kb cells (Sherman et al, Science 258:815-818, 1992) and 3 x 106/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20U/ml IL-2. Cells continued to be restimulated on a weekly basis as described, in preparation for cloning the line.

P2S#12 line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells

as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, clones that were growing were isolated and maintained in culture. Several of these clones demonstrated significantly higher reactivity (lysis) against human fibroblasts (HLA A2.1 expressing) transduced with P502S than against control fibroblasts. An example is presented in Figure 1.

This data indicates that P2S #12 represents a naturally processed epitope of the P502S protein that is expressed in the context of the human HLA A2.1 molecule.

6.2. This Example illustrates the preparation of murine CTL lines and CTL clones specific for cells expressing the P501S gene.

This series of experiments were performed similarly to that described above. Mice were immunized with the P1S#10 peptide (SEQ ID NO: 337), which is derived from the P501S gene (also referred to herein as L1-12, SEQ ID NO: 110). The P1S#10 peptide was derived by analysis of the predicted polypeptide sequence for P501S for potential HLA-A2 binding sequences as defined by published HLA-A2 binding motifs (Parker, KC, et al, J. Immunol., 152:163, 1994). P1S#10 peptide was synthesized as described in Example 4, and empirically tested for HLA-A2 binding using a T cell based competition assay. Predicted A2 binding peptides were tested for their ability to compete HLA-A2 specific peptide presentation to an HLA-A2 restricted CTL clone (D150M58), which is specific for the HLA-A2 binding influenza matrix peptide fluM58. D150M58 CTL secretes TNF in response to self-presentation of peptide fluM58. In the competition assay, test peptides at 100-200 µg/ml were added to cultures of D150M58 CTL in order to bind HLA-A2 on the CTL. After thirty minutes, ·CTL cultured with test peptides, or control peptides, were tested for their antigen dose response to the fluM58 peptide in a standard TNF bioassay. As shown in Figure 3, peptide P1S#10 competes HLA-A2 restricted presentation of fluM58, demonstrating that peptide P1S#10 binds HLA-A2.

Mice expressing the transgene for human HLA A2.1 were immunized as described by Theobald et al. (*Proc. Natl. Acad. Sci. USA 92*:11993-11997, 1995) with the following modifications. Mice were immunized with 62.5μg of P1S #10 and 120μg

of an I-A<sup>b</sup> binding peptide derived from Hepatitis B Virus protein emulsified in incomplete Freund's adjuvant. Three weeks later these mice were sacrificed and single cell suspensions prepared using a nylon mesh. Cells were then resuspended at 6 x 10<sup>6</sup> cells/ml in complete media (as described above) and cultured in the presence of irradiated (3000 rads) P1S#10-pulsed (2μg/ml P1S#10 and 10mg/ml β2-microglobulin) LPS blasts (A2 transgenic spleens cells cultured in the presence of 7μg/ml dextran sulfate and 25μg/ml LPS for 3 days). Six days later cells (5 x 10<sup>5</sup>/ml) were restimulated with 2.5 x 10<sup>6</sup>/ml peptide-pulsed irradiated (20,000 rads) EL4A2Kb cells, as described above, and 3 x 10<sup>6</sup>/ml A2 transgenic spleen feeder cells. Cells were cultured in the presence of 20 U/ml IL-2. Cells were restimulated on a weekly basis in preparation for cloning. After three rounds of *in vitro* stimulations, one line was generated that recognized P1S#10-pulsed Jurkat A2Kb targets and P501S-transduced Jurkat targets as shown in Figure 4.

A P1S#10-specific CTL line was cloned by limiting dilution analysis with peptide pulsed EL4 A2Kb tumor cells (1 x 10<sup>4</sup> cells/ well) as stimulators and A2 transgenic spleen cells as feeders (5 x 10<sup>5</sup> cells/ well) grown in the presence of 30U/ml IL-2. On day 14, cells were restimulated as before. On day 21, viable clones were isolated and maintained in culture. As shown in Figure 5, five of these clones demonstrated specific cytolytic reactivity against P501S-transduced Jurkat A2Kb targets. This data indicates that P1S#10 represents a naturally processed epitope of the P501S protein that is expressed in the context of the human HLA-A2.1 molecule.

# EXAMPLE 7 ABILITY OF HUMAN T CELLS TO RECOGNIZE PROSTATE TUMOR POLYPEPTIDES

This Example illustrates the ability of T cells specific for a prostate tumor polypeptide to recognize human tumor.

Human CD8<sup>+</sup> T cells were primed in vitro to the P2S-12 peptide (SEO ID NO: 306) derived from P502S (also referred to as J1-17) using dendritic cells according to the protocol of Van Tsai et al. (Critical Reviews in Immunology 18:65-75, 1998). The resulting CD8<sup>+</sup> T cell microcultures were tested for their ability to recognize the P2S-12 peptide presented by autologous fibroblasts or fibroblasts which were transduced to express the P502S gene in a γ-interferon ELISPOT assay (see Lalvani et al., J. Exp. Med. 186:859-865, 1997). Briefly, titrating numbers of T cells were assayed in duplicate on  $10^4$  fibroblasts in the presence of 3  $\mu$ g/ml human  $\beta_2$ microglobulin and 1 µg/ml P2S-12 peptide or control E75 peptide. In addition, T cells were simultaneously assayed on autologous fibroblasts transduced with the P502S gene or as a control, fibroblasts transduced with HER-2/neu. Prior to the assay, the fibroblasts were treated with 10 ng/ml  $\gamma$ -interferon for 48 hours to upregulate class I MHC expression. One of the microcultures (#5) demonstrated strong recognition of both peptide pulsed fibroblasts as well as transduced fibroblasts in a y-interferon ELISPOT assay. Figure 2A demonstrates that there was a strong increase in the number of y-interferon spots with increasing numbers of T cells on fibroblasts pulsed with the P2S-12 peptide (solid bars) but not with the control E75 peptide (open bars). This shows the ability of these T cells to specifically recognize the P2S-12 peptide. As shown in Figure 2B, this microculture also demonstrated an increase in the number of γinterferon spots with increasing numbers of T cells on fibroblasts transduced to express the P502S gene but not the HER-2/neu gene. These results provide additional confirmatory evidence that the P2S-12 peptide is a naturally processed epitope of the P502S protein. Furthermore, this also demonstrates that there exists in the human T cell repertoire, high affinity T cells which are capable of recognizing this epitope. These T cells should also be capable of recognizing human tumors which express the P502S gene.

### **EXAMPLE 8**

### PRIMING OF CTL *IN VIVO* USING NAKED DNA IMMUNIZATION WITH A PROSTATE ANTIGEN

The prostate tumor antigen L1-12, as described above, is also referred to as P501S. HLA A2Kb Tg mice (provided by Dr L. Sherman, The Scripps Research Institute, La Jolla, CA) were immunized with 100 µg VR10132-P501S either intramuscularly or intradermally. The mice were immunized three times, with a two week interval between immunizations. Two weeks after the last immunization, immune spleen cells were cultured with Jurkat A2Kb-P501S transduced stimulator cells. CTL lines were stimulated weekly. After two weeks of *in vitro* stimulation, CTL activity was assessed against P501S transduced targets. Two out of 8 mice developed strong anti-P501S CTL responses. These results demonstrate that P501S contains at least one naturally processed A2-restricted CTL epitope.

### **EXAMPLE 9**

## GENERATION OF HUMAN CTL *IN VITRO* USING WHOLE GENE PRIMING AND STIMULATION TECHNIQUES WITH PROSTATE TUMOR ANTIGEN

Using *in vitro* whole-gene priming with P501S-retrovirally transduced autologous fibroblasts (see, for example, Yee et al, *The Journal of Immunology*, 157(9):4079-86, 1996), human CTL lines were derived that specifically recognize autologous fibroblasts transduced with P501S (also known as L1-12), as determined by interferon-γ ELISPOT analysis as described above. Using a panel of HLA-mismatched fibroblast lines transduced with P501S, these CTL lines were shown to be restricted HLA-A2 class I allele. Specifically, dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by growing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, DC were infected overnight with recombinant P501S vaccinia virus at a multiplicity of infection (M.O.I) of five, and matured

overnight by the addition of 3 μg/ml CD40 ligand. Virus was inactivated by UV irradiation. CD8+ T cells were isolated using a magnetic bead system, and priming cultures were initiated using standard culture techniques. Cultures were restimulated every 7-10 days using autologous primary fibroblasts retrovirally transduced with P501S. Following four stimulation cycles, CD8+ T cell lines were identified that specifically produced interferon-γ when stimulated with P501S-transduced autologous fibroblasts. The P501S-specific activity could be sustained by the continued stimulation of the cultures with P501S-transduced fibroblasts in the presence of IL-15. A panel of HLA-mismatched fibroblast lines transduced with P501S were generated to define the restriction allele of the response. By measuring interferon-γ in an ELISPOT assay, the P501S specific response was shown to be restricted by HLA-A2. These results demonstrate that a CD8+ CTL response to P501S can be elicited.

### **EXAMPLE 10**

## IDENTIFICATION OF A NATURALLY PROCESSED CTL EPITOPE CONTAINED WITHIN A PROSTATE TUMOR ANTIGEN

The 9-mer peptide p5 (SEQ ID NO: 338) was derived from the P703P antigen (also referred to as P20). The p5 peptide is immunogenic in human HLA-A2 donors and is a naturally processed epitope. Antigen specific CD8+ T cells can be primed following repeated *in vitro* stimulations with monocytes pulsed with p5 peptide. These CTL specifically recognize p5-pulsed target cells in both ELISPOT (as described above) and chromium release assays. Additionally, immunization of HLA-A2 transgenic mice with p5 leads to the generation of CTL lines which recognize a variety of P703P transduced target cells expressing either HLA-A2Kb or HLA-A2. Specifically, HLA-A2 transgenic mice were immunized subcutaneously in the footpad with 100 µg of p5 peptide together with 140 µg of hepatitis B virus core peptide (a Th peptide) in Freund's incomplete adjuvant. Three weeks post immunization, spleen cells from immunized mice were stimulated *in vitro* with peptide-pulsed LPS blasts. CTL activity was assessed by chromium release assay five days after primary *in vitro* 

stimulation. Retrovirally transduced cells expressing the control antigen P703P and HLA-A2Kb were used as targets. CTL lines that specifically recognized both p5-pulsed targets as well as P703P-expressing targets were identified.

Human *in vitro* priming experiments demonstrated that the p5 peptide is immunogenic in humans. Dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal human donors by culturing for five days in RPMI medium containing 10% human serum, 50 ng/ml human GM-CSF and 30 ng/ml human IL-4. Following culture, the DC were pulsed with p5 peptide and cultured with GM-CSF and IL-4 together with CD8+ T cell enriched PBMC. CTL lines were restimulated on a weekly basis with p5-pulsed monocytes. Five to six weeks after initiation of the CTL cultures, CTL recognition of p5-pulsed target cells was demonstrated.

# EXAMPLE 11 EXPRESSION OF A BREAST TUMOR-DERIVED ANTIGEN IN PROSTATE

Isolation of the antigen B305D from breast tumor by differential display is described in US Patent Application No. 08/700,014, filed August 20, 1996. Several different splice forms of this antigen were isolated. The determined cDNA sequences for these splice forms are provided in SEQ ID NO: 366-375, with the predicted amino acid sequences corresponding to the sequences of SEQ ID NO: 292, 298 and 301-303 being provided in SEQ ID NO: 299-306, respectively.

The expression levels of B305D in a variety of tumor and normal tissues were examined by real time PCR and by Northern analysis. The results indicated that B305D is highly expressed in breast tumor, prostate tumor, normal prostate tumor and normal testes, with expression being low or undetectable in all other tissues examined (colon tumor, lung tumor, ovary tumor, and normal bone marrow, colon, kidney, liver, lung, ovary, skin, small intestine, stomach).

### **EXAMPLE 12**

## ELICITATION OF PROSTATE TUMOR ANTIGEN-SPECIFIC CTL RESPONSES IN HUMAN BLOOD

This Example illustrates the ability of a prostate tumor antigen to elicit a CTL response in blood of normal humans.

Autologous dendritic cells (DC) were differentiated from monocyte cultures derived from PBMC of normal donors by growth for five days in RPMI medium containing 10% human serum, 50 ng/ml GMCSF and 30 ng/ml IL-4. Following culture, DC were infected overnight with recombinant P501S-expressing vaccinia virus at an M.O.I. of 5 and matured for 8 hours by the addition of 2 micrograms/ml CD40 ligand. Virus was inactivated by UV irradiation, CD8+ cells were isolated by positive selection using magnetic beads, and priming cultures were initiated in 24-well plates. Following five stimulation cycles, CD8+ lines were identified that specifically produced interferon-gamma when stimulated with autologous P501Stransduced fibroblasts. The P501S-specific activity of cell line 3A-1 could be maintained following additional stimulation cycles on autologous B-LCL transduced with P501S. Line 3A-1 was shown to specifically recognize autologous B-LCL transduced to express P501S, but not EGFP-transduced autologous B-LCL, as measured by cytotoxity assays (51Cr release) and interferon-gamma production (Interferon-gamma Elispot; see above and Lalvani et al., J. Exp. Med. 186:859-865, 1997). The results of these assays are presented in Figures 6A and 6B.

# EXAMPLE 13 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of certain prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 372 clones were identified, and 319 were successfully sequenced. Table I presents a summary of these clones, which are shown in SEQ ID NOs:385-400. Of these sequences SEQ ID NOs:386, 389, 390 and 392 correspond to novel genes, and SEQ ID NOs: 393 and 396 correspond to previously identified sequences. The others (SEQ ID NOs:385, 387, 388, 391, 394, 395 and 397-400) correspond to known sequences, as shown in Table I.

Table I
Summary of Prostate Tumor Antigens

Known Genes	Previously identified Genes	Novel Genes
T-cell gamma chain	P504S	23379 (SEQ ID NO:389)
Kallikrein	P1000C	23399 (SEQ ID NO:392)
Vector	P501S	23320 (SEQ ID NO:386)
CGI-82 protein mRNA (23319; SEQ ID NO:385)	P503S	23381 (SEQ ID NO:390)
PSA ,	P510S	
Ald. 6 Dehyd.	P784P	
L-iditol-2 dehydrogenase (23376; SEQ ID NO:388)	P502S	
Ets transcription factor PDEF (22672; SEQ ID NO:398)	P706P	
hTGR (22678; SEQ ID NO:399)	19142.2, bangur.seq (22621; SEQ ID NO:396)	
KIAA0295(22685; SEQ ID NO:400)	5566.1 Wang(23404; SEQ 1D NO:393)	
Prostatic Acid Phosphatase(22655; SEQ ID NO:397)	P712P	
transglutaminase (22611; SEQ ID NO:395)	P778P	
HDLBP (23508; SEQ ID NO:394)		
CGI-69 Protein(23367; SEQ ID NO:387)		
KIAA0122(23383; SEQ ID NO:391)		
TEEG		

CGI-82 showed 4.06 fold over-expression in prostate tissues as

compared to other normal tissues tested. It was over-expressed in 43% of prostate tumors, 25% normal prostate, not detected in other normal tissues tested. L-iditol-2 dehydrogenase showed 4.94 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 90% of prostate tumors, 100% of normal prostate, and not detected in other normal tissues tested. Ets transcription factor PDEF showed 5.55 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% prostate tumors, 25% normal prostate and not detected in other normal tissues tested. hTGR1 showed 9.11 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 63% of prostate tumors and is not detected in normal tissues tested including normal prostate. KIAA0295 showed 5.59 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 47% of prostate tumors, low to undetectable in normal tissues tested including normal prostate tissues. Prostatic acid phosphatase showed 9.14 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 67% of prostate tumors, 50% of normal prostate, and not detected in other normal tissues tested. Transglutaminase showed 14.84 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 30% of prostate tumors, 50% of normal prostate, and is not detected in other normal tissues tested. High density lipoprotein binding protein (HDLBP) showed 28.06 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% of normal prostate, and is undetectable in all other normal tissues tested. CGI-69 showed 3.56 fold over-expression in prostate tissues as compared to other normal tissues tested. It is a low abundant gene, detected in more than 90% of prostate tumors, and in 75% normal The expression of this gene in normal tissues was very low. prostate tissues. KIAA0122 showed 4.24 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 57% of prostate tumors, it was undetectable in all normal tissues tested including normal prostate tissues. 19142.2 bangur showed 23.25 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors and 100% of

showed 3.31 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 97% of prostate tumors, 75% normal prostate and was also over-expressed in normal bone marrow, pancreas, and activated PBMC. Novel clone 23379 showed 4.86 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in 97% of prostate tumors and 75% normal prostate and is undetectable in all other normal tissues tested. Novel clone 23399 showed 4.09 fold over-expression in prostate tissues as compared to other normal tissues tested. It was over-expressed in 27% of prostate tumors and was undetectable in all normal tissues tested including normal prostate tissues. Novel clone 23320 showed 3.15 fold over-expression in prostate tissues as compared to other normal tissues tested. It was detectable in all prostate tumors and 50% of normal prostate tissues. It was also expressed in normal colon and trachea. Other normal tissues do not express this gene at high level.

# EXAMPLE 14 IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY ELECTRONIC SUBTRACTION

This Example describes the use of an electronic subtraction technique to identify prostate tumor antigens.

Potential prostate-specific genes present in the GenBank human EST database were identified by electronic subtraction (similar to that described by Vasmatizis et al., *Proc. Natl. Acad. Sci. USA 95*:300-304, 1998). The sequences of EST clones (43,482) derived from various prostate libraries were obtained from the GenBank public human EST database. Each prostate EST sequence was used as a query sequence in a BLASTN (National Center for Biotechnology Information) search against the human EST database. All matches considered identical (length of matching sequence >100 base pairs, density of identical matches over this region > 70%) were grouped

(aligned) together in a cluster. Clusters containing more than 200 ESTs were discarded since they probably represented repetitive elements or highly expressed genes such as those for ribosomal proteins. If two or more clusters shared common ESTs, those clusters were grouped together into a "supercluster," resulting in 4,345 prostate superclusters.

Records for the 479 human cDNA libraries represented in the GenBank release were downloaded to create a database of these cDNA library records. These 479 cDNA libraries were grouped into three groups, Plus (normal prostate and prostate tumor libraries, and breast cell lines, in which expression was desired), Minus (libraries from other normal adult tissues, in which expression was not desirable), and Other (fetal tissue, infant tissue, tissues found only in women, non-prostate tumors and cell lines other than prostate cell lines, in which expression was considered to be irrelevant). A summary of these library groups is presented in Table II.

<u>Table II</u> <u>Prostate cDNA Libraries and ESTs</u>

Library	# of Libraries	# of ESTs
Plus	25	43,482
Normal	11	18,875
Tumor	11	21,769
Cell lines	3	2,838
Minus	166	
Other	287	

Each supercluster was analyzed in terms of the ESTs within the supercluster. The tissue source of each EST clone was noted and used to classify the superclusters into four groups: Type 1- EST clones found in the Plus group libraries only; no expression detected in Minus or Other group libraries; Type 2- EST clones found in the Plus and Other group libraries only; no expression detected in the Minus group; Type 3- EST clones found in the Plus, Minus and Other group libraries, but the

expression in the Plus group is higher than in either the Minus or Other groups; and Type 4- EST clones found in Plus, Minus and Other group libraries, but the expression in the Plus group is higher than the expression in the Minus group. This analysis identified 4,345 breast clusters (*see* Table III). From these clusters, 3,172 EST clones were ordered from Research Genetics, Inc., and were received as frozen glycerol stocks in 96-well plates.

<u>Table III</u>
Prostate Cluster <u>Summary</u>

Туре	# of Superclusters	# of ESTs Ordered
1	688	677
2	2899	2484
3	85	11
4	673	0
Total	4345	3172

The inserts were PCR-amplified using amino-linked PCR primers for Synteni microarray analysis. When more than one PCR product was obtained for a particular clone, that PCR product was not used for expression analysis. In total, 2,528 clones from the electronic subtraction method were analyzed by microarray analysis to identify electronic subtraction breast clones that had high tumor vs. normal tissue mRNA. Such screens were performed using a Synteni (Palo Alto, CA) microarray, according to the manufacturer's instructions (and essentially as described by Schena et al., *Proc. Natl. Acad. Sci. USA 93*:10614-10619, 1996 and Heller et al., *Proc. Natl. Acad. Sci. USA 94*:2150-2155, 1997). Within these analyses, the clones were arrayed on the chip, which was then probed with fluorescent probes generated from normal and tumor prostate cDNA, as well as various other normal tissues. The slides were scanned and the fluorescence intensity was measured.

Clones with an expression ratio greater than 3 (i.e., the level in prostate tumor cDNA was at least three times the level in normal prostate cDNA) were

identified as prostate tumor-specific sequences (Table IV). The sequences of these clones are provided in SEQ ID NOs:401-453, with certain novel sequences shown in SEQ ID NOs:407, 413, 416-419, 422, 426, 427 and 450.

<u>Table IV</u>

<u>Prostate-tumor Specific Clones</u>

SEQ ID NO.	Sequence	Comments
	Designation	
401	22545	previously identified P1000C
402	22547	previously identified P704P
403	22548	known
404	22550	known
405	22551	PSA
406	22552	prostate secretory protein 94
407	22553	novel
408	22558	previously identified P509S
409	22562	glandular kallikrein
410	22565	previously identified P1000C
411	22567	PAP
412	22568	B1006C (breast tumor antigen)
413	22570	novel
414	22571	PSA
415	22572	previously identified P706P
416	22573	novel
417	22574	novel
418	22575	novel
419	22580	novel
420	22581	PAP
421	22582	prostatic secretory protein 94
422	22583	novel
423	22584	prostatic secretory protein 94
424	22585	prostatic secretory protein 94
425	22586	known
426	22587	novel _
427	22588	novel
428	22589	PAP
429	22590	known
430	22591	PSA
431	22592	known
432	22593	Previously identified P777P

433	22594	T cell receptor gamma chain	
434	22595	Previously identified P705P	
435	22596	Previously identified P707P	
436	22847	PAP	
437	22848	known	
438	22849	prostatic secretory protein 57	
439	22851	PAP	
440	22852	PAP	
441	22853	PAP	
442	22854	previously identified P509S	
443	22855	previously identified P705P	
444	22856	previously identified P774P	
445	22857	PSA	
446	23601	previously identified P777P	
447	23602	PSA	
448	23605	PSA	
449	23606	PSA	
450	23612	novel	
451	23614	PSA	
452	23618	previously identified P1000C	
453	23622	previously identified P705P	

# EXAMPLE 15 FURTHER IDENTIFICATION OF PROSTATE TUMOR ANTIGENS BY MICROARRAY ANALYSIS

This Example describes the isolation of additional prostate tumor polypeptides from a prostate tumor cDNA library.

A human prostate tumor cDNA expression library as described above was screened using microarray analysis to identify clones that display at least a three fold over-expression in prostate tumor and/or normal prostate tissue, as compared to non-prostate normal tissues (not including testis). 142 clones were identified and sequenced. Certain of these clones are shown in SEQ ID NOs:454-467. Of these sequences SEQ ID NOs:459-461 correspond to novel genes. The others (SEQ ID NOs:454-458 and 461-467) correspond to known sequences.

### **EXAMPLE 16**

### FURTHER CHARACTERIZATION OF PROSTATE TUMOR ANTIGEN P710P

This Example describes the full length cloning of P710P.

The prostate cDNA library described above was screened with the P710P fragment described above. One million colonies were plated on LB/Ampicillin plates. Nylon membrane filters were used to lift these colonies, and the cDNAs picked up by these filters were then denatured and cross-linked to the filters by UV light. The P710P fragment was radiolabeled and used to hybridize with the filters. Positive cDNA clones were selected and their cDNAs recovered and sequenced by an automatic ABI Sequencer. Four sequences were obtained, and are presented in SEQ ID NOs:468-471.

From the foregoing, it will be appreciated that, although specific embodiments of the invention have been described herein for the purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the present invention is not limited except as by the appended claims.

### **CLAIMS**

- 1. An isolated polypeptide comprising at least an immunogenic portion of a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (a) sequences recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472;
- (b) sequences that hybridize to any of the foregoing sequences under moderately stringent conditions; and
  - (c) complements of any of the sequence of (a) or (b).
- 2. An isolated polypeptide according to claim 1, wherein the polypeptide comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotide sequences.
- 3. An isolated polypeptide comprising a sequence recited in any one of SEQ ID NO: 108, 112, 113, 114, 172, 176, 178, 327, 329, 331, 339 and 383.
- 4. An isolated polynucleotide encoding at least 15 amino acid residues of a prostate tumor protein, or a variant thereof that differs in one or more

substitutions, deletions, additions and/or insertions such that the ability of the variant to react with antigen-specific antisera is not substantially diminished, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.

- 5. An isolated polynucleotide encoding a prostate tumor protein, or a variant thereof, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing sequences.
- 6. An isolated polynucleotide comprising a sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
- 7. An isolated polynucleotide comprising a sequence that hybridizes, under moderately stringent conditions, to a sequence recited in any one of

SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.

- 8. An isolated polynucleotide complementary to a polynucleotide according to any one of claims 4-7.
- 9. An expression vector comprising a polynucleotide according to any one of claims 4-7.
- 10. A host cell transformed or transfected with an expression vector according to claim 9.
- 11. An expression vector comprising a polynucleotide according claim 8.
- 12. A host cell transformed or transfected with an expression vector according to claim 11.
- 13. A pharmaceutical composition comprising a polypeptide according to claim 1, in combination with a physiologically acceptable carrier.
- 14. A vaccine comprising a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 15. A vaccine according to claim 14, wherein the non-specific immune response enhancer is an adjuvant.

16. A vaccine according to claim 14, wherein the non-specific immune response enhancer induces a predominantly Type I response.

- 17. A pharmaceutical composition comprising a polynucleotide according to claim 4, in combination with a physiologically acceptable carrier.
- 18. A vaccine comprising a polynucleotide according to claim 4, in combination with a non-specific immune response enhancer.
- 19. A vaccine according to claim 18, wherein the non-specific immune response enhancer is an adjuvant.
- 20. A vaccine according to claim 18, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 21. An isolated antibody, or antigen-binding fragment thereof, that specifically binds to a prostate tumor protein that comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472 or a complement of any of the foregoing polynucleotide sequences.
- 22. A pharmaceutical composition comprising an antibody or fragment thereof according to claim 18, in combination with a physiologically acceptable carrier.

23. A pharmaceutical composition comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a pharmaceutically acceptable carrier or excipient.

- 24. A pharmaceutical composition according to claim 23, wherein the antigen presenting cell is a dendritic cell or a macrophage.
- 25. A vaccine comprising an antigen-presenting cell that expresses a polypeptide according to claim 1, in combination with a non-specific immune response enhancer.
- 26. A vaccine according to claim 25, wherein the non-specific immune response enhancer is an adjuvant.
- 27. A vaccine according to claim 25, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 28. A vaccine according to claim 25, wherein the antigen-presenting cell is a dendritic cell.
- 29. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 30. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a polynucleotide according to claim 4, and thereby inhibiting the development of a cancer in the patient.
- 31. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antibody or antigen-

binding fragment thereof according to claim 21, and thereby inhibiting the development of a cancer in the patient.

- 32. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of an antigen-presenting cell that expresses a polypeptide according to claim 1, and thereby inhibiting the development of a cancer in the patient.
- 33. A method according to claim 32, wherein the antigen-presenting cell is a dendritic cell.
- 34. A method according to any one of claims 29-32, wherein the cancer is prostate cancer.
- 35. A fusion protein comprising at least one polypeptide according to claim 1.
- 36. A fusion protein according to claim 35, wherein the fusion protein comprises an expression enhancer that increases expression of the fusion protein in a host cell transfected with a polynucleotide encoding the fusion protein.
- 37. A fusion protein according to claim 35, wherein the fusion protein comprises a T helper epitope that is not present within the polypeptide of claim 1.
- 38. A fusion protein according to claim 35, wherein the fusion protein comprises an affinity tag.
- 39. An isolated polynucleotide encoding a fusion protein according to claim 35.

40. A pharmaceutical composition comprising a fusion protein according to claim 32, in combination with a physiologically acceptable carrier.

- 41. A vaccine comprising a fusion protein according to claim 35, in combination with a non-specific immune response enhancer.
- 42. A vaccine according to claim 41, wherein the non-specific immune response enhancer is an adjuvant.
- 43. A vaccine according to claim 41, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 44. A pharmaceutical composition comprising a polynucleotide according to claim 40, in combination with a physiologically acceptable carrier.
- 45. A vaccine comprising a polynucleotide according to claim 40, in combination with a non-specific immune response enhancer.
- 46. A vaccine according to claim 45, wherein the non-specific immune response enhancer is an adjuvant.
- 47. A vaccine according to claim 45, wherein the non-specific immune response enhancer induces a predominantly Type I response.
- 48. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a pharmaceutical composition according to claim 40 or claim 44.

49. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a vaccine according to claim 41 or claim 45.

- 50. A method for removing tumor cells from a biological sample, comprising contacting a biological sample with T cells that specifically react with a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
- (ii) complements of the foregoing polynucleotides; wherein the step of contacting is performed under conditions and for a time sufficient to permit the removal of cells expressing the prostate tumor protein from the sample.
- 51. A method according to claim 50, wherein the biological sample is blood or a fraction thereof.
- 52. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient a biological sample treated according to the method of claim 50.
- 53. A method for stimulating and/or expanding T cells specific for a prostate tumor protein, comprising contacting T cells with one or more of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence provided in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); and/or

(iv) an antigen presenting cell that expresses a polypeptide of (i) or (ii);

under conditions and for a time sufficient to permit the stimulation and/or expansion of T cells.

- 54. An isolated T cell population, comprising T cells prepared according to the method of claim 53.
- 55. A method for inhibiting the development of a cancer in a patient, comprising administering to a patient an effective amount of a T cell population according to claim 54.
- 56. A method for inhibiting the development of a cancer in a patient, comprising the steps of:
- (a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:
  - (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate; and

- (b) administering to the patient an effective amount of the proliferated T cells, and thereby inhibiting the development of a cancer in the patient.
- 57. A method for inhibiting the development of a cancer in a patient, comprising the steps of:

(a) incubating CD4<sup>+</sup> and/or CD8+ T cells isolated from a patient with at least one component selected from the group consisting of:

- (i) a polypeptide according to claim 1;
- (ii) a polypeptide encoded by a polynucleotide comprising a sequence of any one of SEQ ID NOs: 1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472;
  - (iii) a polynucleotide encoding a polypeptide of (i) or (ii); or
- (iv) an antigen-presenting cell that expresses a polypeptide of (i) or (ii);

such that T cells proliferate;

- (b) cloning at least one proliferated cell; and
- (c) administering to the patient an effective amount of the cloned T cells, and thereby inhibiting the development of a cancer in the patient.
- 58. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence selected from the group consisting of:
- (i) polynucleotides recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472; and
  - (ii) complements of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent; and
- (c) comparing the amount of polypeptide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.

59. A method according to claim 58, wherein the binding agent is an antibody.

- 60. A method according to claim 59, wherein the antibody is a monoclonal antibody.
- 61. A method according to claim 58, wherein the cancer is prostate cancer.
- 62. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient at a first point in time with a binding agent that binds to a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of polypeptide that binds to the binding agent;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polypeptide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 63. A method according to claim 62, wherein the binding agent is an antibody.
- 64. A method according to claim 63, wherein the antibody is a monoclonal antibody.

65. A method according to claim 62, wherein the cancer is a prostate cancer.

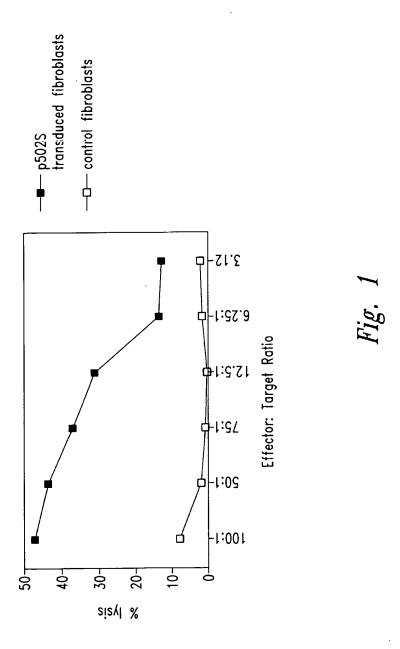
- 66. A method for determining the presence or absence of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;
- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide; and
- (c) comparing the amount of polynucleotide that hybridizes to the oligonucleotide to a predetermined cut-off value, and therefrom determining the presence or absence of a cancer in the patient.
- 67. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 68. A method according to claim 66, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
- 69. A method for monitoring the progression of a cancer in a patient, comprising the steps of:
- (a) contacting a biological sample obtained from a patient with an oligonucleotide that hybridizes to a polynucleotide that encodes a prostate tumor

protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:1-111, 115-171, 173-175, 177, 179-305, 307-315, 326, 328, 330, 332-335, 340-375, 381, 382 or 384-472, or a complement of any of the foregoing polynucleotides;

- (b) detecting in the sample an amount of a polynucleotide that hybridizes to the oligonucleotide;
- (c) repeating steps (a) and (b) using a biological sample obtained from the patient at a subsequent point in time; and
- (d) comparing the amount of polynucleotide detected in step (c) to the amount detected in step (b) and therefrom monitoring the progression of the cancer in the patient.
- 70. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a polymerase chain reaction.
- 71. A method according to claim 69, wherein the amount of polynucleotide that hybridizes to the oligonucleotide is determined using a hybridization assay.
  - 72. A diagnostic kit, comprising:
  - (a) one or more antibodies according to claim 21; and
  - (b) a detection reagent comprising a reporter group.
- 73. A kit according to claim 72, wherein the antibodies are immobilized on a solid support.
- 74. A kit according to claim 73, wherein the solid support comprises nitrocellulose, latex or a plastic material.

75. A kit according to claim 72, wherein the detection reagent comprises an anti-immunoglobulin, protein G, protein A or lectin.

- 76. A kit according to claim 72, wherein the reporter group is selected from the group consisting of radioisotopes, fluorescent groups, luminescent groups, enzymes, biotin and dye particles.
- 77. An oligonucleotide comprising 10 to 40 nucleotides that hybridize under moderately stringent conditions to a polynucleotide that encodes a prostate tumor protein, wherein the tumor protein comprises an amino acid sequence that is encoded by a polynucleotide sequence recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472, or a complement of any of the foregoing polynucleotides.
- 78. A oligonucleotide according to claim 77, wherein the oligonucleotide comprises 10-40 nucleotides recited in any one of SEQ ID NOs:2, 3, 8-29, 41-45, 47-52, 54-65, 70, 73-74, 79, 81, 87, 90, 92, 93, 97, 103, 104, 107, 109-111, 115-160, 171, 173-175, 177, 181, 188, 191, 193, 194, 198, 203, 204, 207, 209, 220, 222-225, 227-305, 307-315, 326, 328, 330, 332, 334, 350-365, 381, 382, 384, 386, 389, 390, 392, 393, 396, 401, 402, 407, 408, 410, 413, 415-419, 422, 426, 427, 432, 434, 435, 442-444, 446, 450, 452, 453, 459-461, 468-471 or 472.
  - 79. A diagnostic kit, comprising:
  - (a) an oligonucleotide according to claim 77; and
- (b) a diagnostic reagent for use in a polymerase chain reaction or hybridization assay.



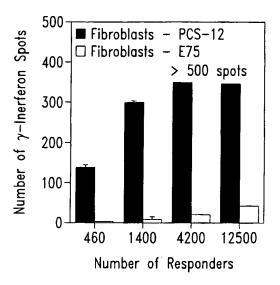


Fig. 2A

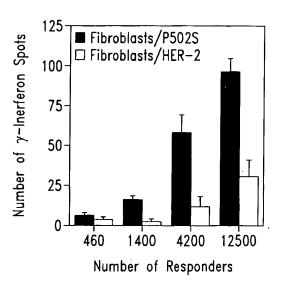
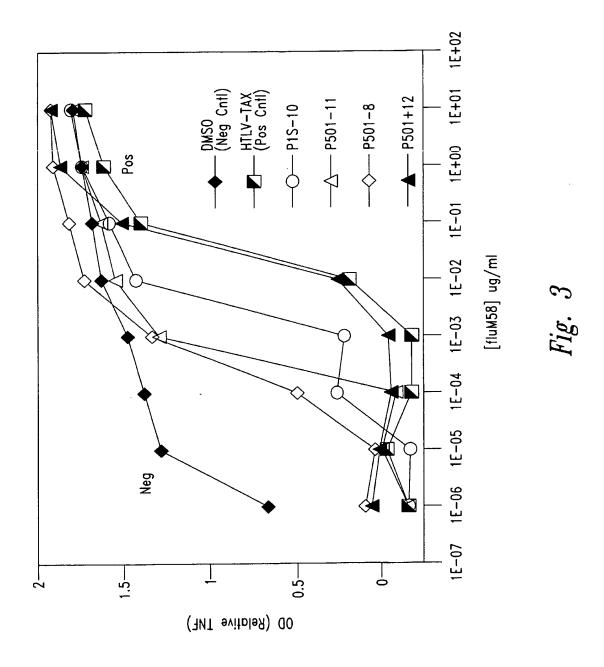
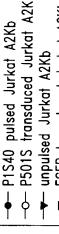


Fig. 2B



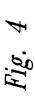
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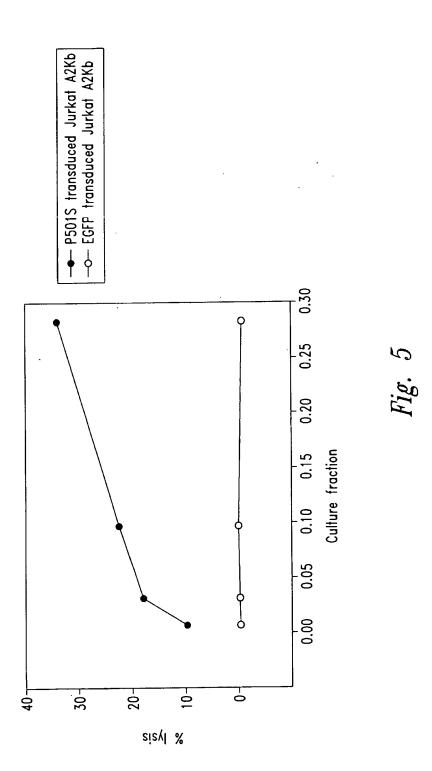
— P1S40 pulsed Jurkat A2Kb
— P501S transduced Jurkat A2Kb

— unpulsed Jurkat A2Kb
— EGFP transduced Jurkat A2Kb



120 100 . 0 Effector Target Ratio .09 40 <u>20</u> -09 50-10-707 40-30-20-0 sisyl %

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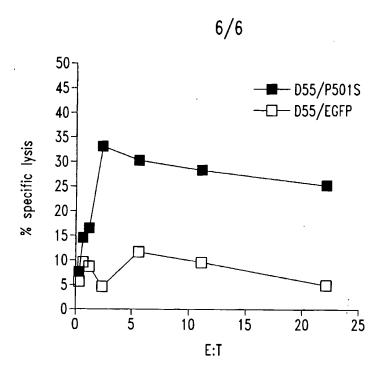


Fig. 6A

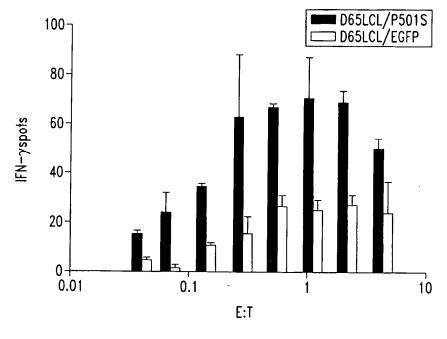


Fig. 6B

PCT/US00/27464

1

## SEQUENCE LISTING

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<110> Corixa Corporation et al.
      <120> COMPOSITIONS AND METHODS FOR THE THERAPY AND
             DIAGNOSIS OF PROSTATE CANCER
      <130> 210121.534PC
      <140> PCT
      <141> 2000-10-04
      <160> 476
      <170> FastSEQ for Windows Version 3.0
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                                                                             300
                                                                             360
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gcgcgcttgg cgtaatcatg gtcataactg tttcctgtgt gaaattgtta tccgctcaca
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anctaactca cattaattgc gttgcgctca ctgnccgctt tccagtcngg aaaactgtcg
                                                                             600
                                                                             660
tgccagctgc attaatgaat cggccaacgc ncggggaaaa gcggtttgcg ttttgggggc
                                                                             720
tetteegett etegeteact nanteetgeg eteggtentt eggetgeggg gaaeggtate
                                                                             780
actoctcaaa ggnggtatta cggttatccn naaatcnggg gatacccngg aaaaaanttt
                                                                             814
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                                                                             120
ctaaagtctg atgaacttcc caatcagatg agcatggatg attggccaga aatgaagaag
                                                                             180
                                                                             240
aagtttqcaq atgtatttqc aaaqaagacg aaggcagagt ggtgtcaaat ctttgacggc
                                                                             300
acaqatqcct qtqtqactcc qgttctqact tttqaqqaqg ttqttcatca tgatcacaac
aaggaacggg getegtttat caccagtgag gageaggaeg tgageeceeg eeetgeacet etgetgttaa acaccecage catecettet tteaaaaggg atceactagt tetagaageg
                                                                             360
                                                                             420
gccgccaccg cggtggagct ccagcttttg ttccctttag tgagggttaa ttgcgcgctt
                                                                             480
```

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ggcgtaatca tggtcatagc tgtttcctgt gtgaaattgt tatccgctca caattccccc
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 aacatacgag ccggaacata aagtgttaag cctggggtgc ctaatgantg agctaactcn
                                                                          600
 cattaattgc gttgcgctca ctgcccgctt tccagtcggg aaaactgtcg tgccactgcn
                                                                          660
 ttantgaatc ngccacccc cgggaaaagg cggttgcntt ttgggcctct tccgctttcc
                                                                          720
 tegeteattg atectngene eeggtetteg getgeggnga aeggtteaet eeteaaagge
                                                                          780
 ggtntnccgg ttatccccaa acnggggata cccnga
                                                                          816
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       <211> 773
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
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tectgetect caetggtgat aaacgageee egtteettgt tgtgateatg atgaacaace
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tcctcaaaag tcagaaccgg agtcacacag gcatctgtgc cgtcaaagat ttgacaccac
                                                                         180
totgocttcg tottctttgc aaatacatct gcaaacttct tottcatttc tggccaatca
                                                                         240
tecatgetea tetgattggg aagtteatea gaetttagte cannteettt gateageage tegtagaaet ggggttetat tgetecaaea geeatgaatt eeccatetge tgteetgtaa
                                                                         300
                                                                         360
gtcgtataga aaggtgctcc accatccaac atgttctgtc ctcgaggggg ggcccggtac
                                                                         420
ccaattegee ctatantgag tegtattacg egegeteact ggeegtegtt ttacaaegte
                                                                         480
gtgactggga aaaccctggg cgttaccaac ttaatcgcct tgcagcacat ccccctttcg
                                                                         540
ccagetggge gtaatanega aaaggeeege accgategee ettecaacag ttgegeacet
                                                                         600
gaatgggnaa atgggacccc cctgttaccg cgcattnaac ccccgcnggg tttngttgtt
                                                                         660
acceccaent nnacegetta caetttgeca gegeettane geeegeteee ttteneettt
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      <210> 4
      <211> 828
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      <221> misc_feature
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                                                                         120
toggaacact ggetgtetet gaagacttet egeteagtit eagtgaggae acacacaaag
                                                                         180
acgtgggtga ccatgttgtt tgtggggtgc agagatggga ggggtggggc ccaccctgga
                                                                         240
agagtggaca gtgacacaag gtggacactc tctacagatc actgaggata agctggagcc
                                                                         300
acaatgcatg aggcacacac acagcaagga tgacnctgta aacatagccc acgctgtcct
                                                                         360
gngggcactg ggaagcctan atnaggccgt gagcanaaag aaggggagga tccactagtt
                                                                         420
ctanagegge egecacegeg gtgganetee anettttgtt eeetttagtg agggttaatt
                                                                         480
gcgcgcttgg cntaatcatg gtcatanctn tttcctgtgt gaaattgtta tccgctcaca
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attocacaca acatacgano oggaaacata aantgtaaac otggggtgco taatgantga
                                                                         600
ctaactcaca ttaattgcgt tgcgctcact gcccgctttc caatcnggaa acctgtcttg
                                                                         660
concttgeat thatgaaten gecaaceee ggggaaaage gtttgegttt tgggegetet
                                                                         720
tecgetteet eneteantta ntecetnene teggteatte eggetgenge aaaceggtte
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accnecteea aagggggtat teeggtttee cenaateegg gganance
                                                                         828
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                                                                       120
                                                                       180
attttataac aatcaacacc tgtggctttt aaaatttggt tttcataaga taatttatac
                                                                       240
tgaagtaaat ctagccatgc ttttaaaaaa tgctttaggt cactccaagc ttggcagtta
acatttggca taaacaataa taaaacaatc acaatttaat aaataacaaa tacaacattg
                                                                       300
                                                                       360
taggccataa tcatatacag tataaggaaa aggtggtagt gttgagtaag cagttattag
aatagaatac cttggcctct atgcaaatat gtctagacac tttgattcac tcagccctga
                                                                       420
cattcagttt tcaaagtagg agacaggttc tacagtatca ttttacagtt tccaacacat
                                                                       480
tgaaaacaag tagaaaatga tgagttgatt tttattaatg cattacatcc tcaagagtta
                                                                       540
                                                                       600
tcaccaaccc ctcagttata aaaaattttc aagttatatt agtcatataa cttggtgtgc
                                                                       660
ttattttaaa ttaqtqctaa atggattaag tgaagacaac aatggtcccc taatgtgatt
                                                                       720
gatattqqtc atttttacca gcttctaaat ctnaactttc aggcttttga actggaacat
tgnatnacag tgttccanag ttncaaccta ctggaacatt acagtgtgct tgattcaaaa
                                                                       780
                                                                       834
tgttattttg ttaaaaatta aattttaacc tggtggaaaa ataatttgaa atna
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      <211> 818
      <212> DNA
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      <220>
      <221> misc_feature
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aaccacatct acaaaatgcc agtatcaggc ggcggcttcg aagccaaagt gatgtttgga
                                                                       120
                                                                       180
tgtaaagtga aatattagtt ggcggatgaa gcagatagtg aggaaagttg agccaataat
                                                                       240
gacqtgaagt ccgtggaagc ctgtggctac aaaaaatgtt gagccgtaga tgccgtcgga
aatggtgaag ggagactcga agtactctga ggcttgtagg agggtaaaat agagacccag
                                                                       300
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                                                                       420
                                                                       480
ttctagggga tttagcgggg tgatgcctgt tgggggccag tgccctccta gttggggggt
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ttantanggc ctantatgaa gaacttttgg antggaatta aatcaatngc ttggccggaa
                                                                       720
gtcattanga nggctnaaaa ggccctgtta ngggtctggg ctnggtttta cccnacccat
                                                                       780
                                                                       818
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      <221> misc_feature
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                                                                       120
cgggccctat ttcaaagatt tttaggggaa ttaattctag gacgatgggt atgaaactgt
ggtttgctcc acagatttca gagcattgac cgtagtatac ccccggtcgt gtagcggtga
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aagtggtttg gtttagacgt ccgggaattg catctgtttt taagcctaat gtggggacag
                                                                          240
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                                                                          300
 gtactactcg attgtcaacg tcaaggagtc gcaggtcgcc tggttctagg aataatgggg
                                                                          360
 gaagtatgta ggaattgaag attaatccgc cgtagtcggt gttctcctag gttcaatacc
                                                                          420
 attggtggcc aattgatttg atggtaaggg gagggatcgt tgaactcgtc tgttatgtaa
                                                                          480
 aggatneett ngggatggga aggenatnaa ggactangga tnaatggegg geangatatt
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 tcaaacngtc tctanttcct gaaacgtctg aaatgttaat aanaattaan tttngttatt
                                                                          600
 gaatnttnng gaaaagggct tacaggacta gaaaccaaat angaaaanta atnntaangg
                                                                          660
 cnttatentn aaaggtnata accnetecta tnateceace caatngnatt ecceaenenn
                                                                          720
 acnattggat necessantte canaaangge enceeeegg tgnanneene ettttgttee
                                                                          780
 cttnantgan ggttattene ecetngentt atcance
                                                                          817
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       <211> 799
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       <213> Homo sapien
       <220>
       <221> misc feature
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ctgaagcgca cgtcccagaa ggtggacttg gcactgaaac agctgggaca catccgcgag
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tgggtggeeg angeetgane egetetgeet tgetgeeece angtgggeeg ceacceeetg
                                                                         240
                                                                         300
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                                                                         360
ggattttgct cctanantaa ggctcatctg ggcctcggcc ccccacctg gttggccttg
                                                                         420
tetttgangt gagececatg tecatetggg ceaetgteng gaceaeettt ngggagtgtt
                                                                         480
ctccttacaa ccacannatg cccggctcct cccggaaacc antcccancc tgngaaggat
                                                                         540
caagneetgn atccactnnt netanaaceg geenceneeg engtggaace encettntgt
                                                                         600
teettttent tnagggttaa tnnegeettg geettneean ngteetnene ntttteennt
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gttnaaattg ttangeneee neennteeen ennennenan eeegaeeenn annttnnann
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neetgggggt neennengat tgaccennee neeetntant tgenttnggg nnenntgeee
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                                                                         799
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cacccatece angacgegge tacactnetg gacetecene tecaccaett teatgegetg
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ttentaceeg egnatntgte ceanetgttt engtgeenae tecanettet nggaegtgeg
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encentantg cacenattee caentttnne agnttteene nnegngette ettntaaaag
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ggttganccc cggaaaatnc cccaaagggg gggggccngg tacccaactn ccccctnata
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gctgaantcc ccatnaccnn gnctcnatgg ancentcent tttaannacn ttctnaactt
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gggaanance etegneenth ecceenttaa teceneettg enangment ecceenntee
                                                                         720
necennntng gentntnann enaaaagge cennnaneaa teteetnnen eeteantteg
                                                                         780
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ccancecteg aaateggeen e
                                                                         801
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                                                                         120
 agatoctgcc ctacacactg gcctccctct accaccggga gaagcaggtg ttcctgccca
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 teetgttaac cecatgggge tgeeggettg geegecaatt tetgttgetg ceaaantnat
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                                                                        780
gangttccc
                                                                        789
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 ctacattaaa cgaagctgca ggttaagggg cttanagatg ggaaaccagg tgactgagtt
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 tattcagctc ccaaaaaccc ttctctaggt gtgtctcaac taggaggcta gctgttaacc
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 ctgagectgg gtaatecace tgeaqagtee eegcatteea gtgeatggaa ceettetgge
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 accccggcac cccnangggg gttaacagga anengggnaa cntggaaccc aattnaggca
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                                                                         120
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                                                                         240
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                                                                         360
                                                                         420
acacttgctc tcagtcttan caccatanca gcccntgaaa accaananca aagaccacna
                                                                         480
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                                                                         540
                                                                         600
agtggcccna aaaatcttca aaaaggatgc cccatcnatt gaccccccaa atgcccactg
ccaacagggg ctgcccacn cncnnaacga tganccnatt gnacaagatc tncntggtct
                                                                         660
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                                                                         751
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accatgcagt gcttcagctt cattaagacc atgatgatcc tcttcaattt gctcatcttt
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                                                                         240
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                                                                         300
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gaggttgcaa tgctgtggtc gccttggtgt acaccacaat ggctgagcac ttcctgacgt
                                                                         480
tgctggtaat gcctgccatc aanaaaagat tatgggttcc caggaanact tcactcaagt
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gttggaacac caccatgaaa gggctcaagt gctgtggctt cnnccaacta tacggatttt
                                                                         600
gaagantcac ctacttcaaa gaaaanagtg cctttccccc atttctgttg caattgacaa
                                                                         660
acgtccccaa cacagccaat tgaaaacctg cacccaaccc aaangggtcc ccaaccanaa
                                                                         720
attnaaggg
                                                                         729
      <210> 14
      <211> 816
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(816)
      <223> n = A, T, C or G
tgctcttcct caaagttgtt cttgttgcca taacaaccac cataggtaaa gcgggcgcag
                                                                          60
tgttcgctga aggggttgta gtaccagcgc gggatgctct ccttgcagag tcctgtgtct
                                                                         120
ggcaggtcca cgcagtgccc tttgtcactg gggaaatgga tgcgctggag ctcgtcaaag
                                                                         180
                                                                         240
ccactcgtgt atttttcaca ggcagcctcg tccgacgcgt cggggcagtt gggggtgtct
tcacactcca ggaaactgtc natgcagcag ccattgctgc agcggaactg ggtgggctga
                                                                         300
cangigecag ageacactgg atggegectt tecatgnnan gggeectgng ggaaagteec
                                                                         360
tgancccan anctgcctct caaangcccc accttgcaca ccccgacagg ctagaatgga
                                                                         420
atcttcttcc cqaaaqqtaq ttnttcttqt tqcccaancc anccccntaa acaaactctt
                                                                         480
gcanatctgc tccgnggggg tcntantacc ancgtgggaa aagaacccca ggcngcgaac
                                                                         540
caancttgtt tggatncgaa gcnataatct nctnttctgc ttggtggaca gcaccantna
                                                                         600
```

```
ctgtnnanct ttagnccntg gtcctcntgg gttgnncttg aacctaatcn ccnntcaact
                                                                       660
qqqacaaqqt aantnqcent cetttnaatt ceenanentn eeceetggtt tggggttttn
                                                                       720
                                                                       780
cncnctccta ccccagaaan nccgtgttcc cccccaacta ggggccnaaa ccnnttnttc
                                                                       816
cacaaccctn ccccacccac gggttcngnt ggttng
      <210> 15
      <211> 783
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (783)
      <223> n = A, T, C or G
      <400> 15
                                                                        60
ccaaggeetg ggeaggeata nacttgaagg tacaacccca ggaacccctg gtgetgaagg
atgtggaaaa cacagattgg cgcctactgc ggggtgacac ggatgtcagg gtagagagga
                                                                       120
aaqacccaaa ccaqqtqqaa ctqtqqqqac tcaaggaang cacctacctg ttccagctga
                                                                       180
                                                                       240
cagtgactag ctcagaccac ccagaggaca cggccaacgt cacagtcact gtgctgtcca
ccaagcagac agaagactac tgcctcgcat ccaacaangt gggtcgctgc cggggctctt
                                                                       300
teccaegetg gtactatgae eccaeggage agatetgeaa gagtttegtt tatggagget
                                                                       360
gcttgggcaa caagaacaac taccttcggg aagaagagtg cattctancc tgtcngggtg
                                                                       420
tgcaaggtgg gcctttgana ngcanctctg gggctcangc gactttcccc cagggcccct
                                                                       480
ccatggaaag gcgccatcca ntgttctctg gcacctgtca gcccacccag ttccgctgca
                                                                       540
ncaatggctg ctgcatcnac antttcctng aattgtgaca acacccccca ntgcccccaa
                                                                       600
ccctcccaac aaagcttccc tgttnaaaaa tacnccantt ggcttttnac aaacncccgg
                                                                       660
                                                                       720
cncctccntt ttccccnntn aacaaagggc nctngcnttt gaactgcccn aacccnggaa
tetneening aaaaantice eeeeetgit eetinaanee eeteenenaa anetneeeee
                                                                       780
                                                                       783
CCC
      <210> 16
      <211> 801
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(801)
      <223> n = A, T, C or G
      <400> 16
gccccaattc cagctgccac accacccacg gtgactgcat tagttcggat gtcatacaaa
                                                                        60
agetgattga ageaaccete tactttttgg tegtgageet tttgettggt geaggtttea
                                                                       120
tiggetgtgt tiggtgaegtt gteattgeaa cagaatgggg gaaaggeact gttetetttg
                                                                       180
aagtagggtg agtcctcaaa atccgtatag ttggtgaagc cacagcactt gagccctttc
                                                                       240
atgqtqqtqt tccacacttg agtgaagtct tcctgggaac cataatcttt cttgatggca
                                                                       300
                                                                       360
ggcactacca gcaacgtcag gaagtgctca gccattgtgg tgtacaccaa ggcgaccaca
gcagctgcaa cctcagcaat gaagatgagg aggaggatga agaagaacgt cncgagggca
                                                                       420
cacttqctct ccqtcttaqc accataqcaq cccangaaac caaqaqcaaa gaccacaacg
                                                                       480
congetgeqa atqaaaqaaa ntacccacqt tgacaaactg catggccact ggacgacagt
                                                                       540
tggcccgaan atcttcagaa aagggatgcc ccatcgattg aacacccana tgcccactgc
                                                                       600
cnacagget geneenenen gaaagaatga gecattgaag aaggatente ntggtettaa
                                                                       660
tgaactgaaa contgoatgg tggcccctgt tcagggctct tggcagtgaa ttctganaaa
                                                                       720
aaggaacngc ntnagccccc ccaaangana aaacaccccc gggtgttgcc ctgaattggc
                                                                       780
                                                                       801
ggccaaggan ccctgccccn g
      <210> 17
      <211> 740
      <212> DNA
      <213> Homo sapien
```

```
<220>
      <221> misc_feature
      <222> (1) ... (740)
      \langle 223 \rangle n = A, T, C or G
      <400> 17
gtgagagcca ggcgtccctc tgcctgccca ctcagtggca acacccggga gctgttttgt
                                                                         60
cetttgtgga geeteageag tteeetettt cagaacteae tgeeaagage eetgaacagg
                                                                        120
agccaccatg cagtgcttca gcttcattaa gaccatgatg atcctcttca atttqctcat
                                                                        180
ctttctgtgt ggtgcagccc tgttggcagt gggcatctgg gtgtcaatcg atggggcatc
                                                                        240
ctttctgaag atcttcgggc cactgtcgtc cagtgccatg cagtttgtca acgtgggcta
                                                                        300
cttcctcatc gcagccggcg ttgtggtctt tgctcttggt ttcctqqgct qctatqqtqc
                                                                        360
taagacggag agcaagtgtg coctcgtgac gttcttcttc atcctcctcc tcatcttcat
                                                                        420
tgctgaagtt gcagctgctg tggtcgcctt ggtgtacacc acaatggctg aaccattcct
                                                                        480
gacgttgctg gtantgcctg ccatcaanaa agattatggg ttcccaggaa aaattcactc
                                                                        540
aantntggaa caccnccatg aaaagggctc caatttctgn tggcttcccc aactataccg
                                                                        600
quattttqaa aganteneee taetteeaaa aaaaaanant tgeetttnee eeenttetgt
                                                                        660
tgcaatgaaa acntcccaan acngccaatn aaaacctgcc cnnncaaaaa ggntcncaaa
                                                                        720
caaaaaant nnaagggttn
                                                                        740
      <210> 18
      <211> 802
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (802)
      <223> n = A, T, C or G
      <400> 18
ccgctggttg cgctggtcca gngnagccac gaagcacgtc agcatacaca gcctcaatca
                                                                         60
caaggtette cagetgeege acattaegea qqqeaaqaqe etecageaac actgeatatq
                                                                        120
ggatacactt tactttagca gccagggtga caactgagag gtgtcgaagc ttattcttct
                                                                        180
gagcctctgt tagtggagga agattccggg cttcagctaa gtagtcagcg tatgtcccat
                                                                        240
aagcaaacac tgtgagcagc cggaaggtag aggcaaagtc actctcagcc agctctctaa
                                                                        300
cattgggcat gtccagcagt tctccaaaca cgtagacacc agnggcctcc agcacctgat
                                                                        360
ggatgagtgt ggccagcgct gcccccttgg ccgacttggc taggagcaga aattgctcct
                                                                        420
ggttctgccc tgtcaccttc acttccgcac tcatcactgc actgagtgtg ggggacttgg
                                                                        480
getcaggatg tecagagacg tggtteegee coetenetta atgacacegn ceanneaace
                                                                        540
gteggeteec geogantgng tregtegine etgggteagg gtetgetgge enetacttge
                                                                        600
aancttogto nggoccatgg aattoacono acoggaactn gtangatoca ctnnttotat
                                                                        660
aaccggncgc caccgcnnnt ggaactccac tettnttncc tttacttgag ggttaaggtc
                                                                        720
accettnncg ttacettggt ccaaacentn centgtgteg anatngtnaa tenggneena
                                                                        780
tnccancene atangaagee ng
                                                                        802
      <210> 19
    . <211> 731
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (731)
      <223> n = A, T, C or G
      <400> 19
cnaagettee aggtnaeggg eegenaance tgaeeenagg tancanaang eagnengegg
                                                                         60
gageceaceg teaegnggng gngtetttat nggaggggge ggagecacat enetggaent
                                                                        120
entgacecca acteceence neneantgea gtgatgagtg cagaactgaa ggtnacgtgg
                                                                        180
caggaaccaa gancaaanne tgeteennte caagteggen nagggggegg ggetggeeae
                                                                        240
geneateent enagtgetgn aaageeeenn eetgtetaet tgtttggaga aengennnga
                                                                        300
```

```
catgcccagn gttanataac nggcngagag tnantttgcc tetecettec ggetgegean
                                                                            360
cgngtntgct tagnggacat aacctgacta cttaactgaa cccnngaatc tnccncccct
                                                                            420
ccactaagct cagaacaaaa aacttcgaca ccactcantt gtcacctgnc tgctcaagta
                                                                            480
aagtgtaccc catneccaat gtntgctnga ngctctqncc tqcnttanqt tcqqtcctqq
                                                                            540
gaagacetat caattnaage tatgtttetg actgeetett geteettgna acaanenace
                                                                            600
 cnncnntcca aggggggnc ggccccaat cccccaacc ntnaattnan tttanccccn
                                                                            660
eccenggee eggeettta enamentenn nnaengggna aaacennnge tttneceaac
                                                                            720
nnaatccncc t
                                                                            731
       <210> 20
       <211> 754
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1)...(754)
       \langle 223 \rangle n = A, T, C or G
       <400> 20
ttttttttt tttttttt taaaaacccc ctccattnaa tgnaaacttc cgaaattgtc
caacccctc ntccaaatnn conttteegg gngggggtte caaacccaan ttanntttgg
                                                                           120
annttaaatt aaatnttnnt tggnggnnna anccnaatgt nangaaagtt naacccanta
                                                                            180
tnancttnaa tncctggaaa ccngtngntt ccaaaaatnt ttaaccctta antccctccg
                                                                            240
aaatngttna nggaaaaccc aanttctcnt aaggttgttt gaaggntnaa tnaaaanccc
                                                                            300
nnccaattgt ttttngccac gcctgaatta attggnttcc gntgttttcc nttaaaanaa
                                                                            360
ggnnancccc ggttantnaa tccccccnnc cccaattata ccganttttt ttngaattgg
                                                                            420
ganceenegg gaattaacgg ggnnnnteee tnttgggggg enggnneece eecenteggg ggttngggne aggnennaat tgtttaaggg teegaaaaat eecteenaga aaaaaanete
                                                                           480
                                                                           540
ccaggntgag nntngggttt ncccccccc canggcccct ctcgnanagt tggggtttgg
                                                                           600
ggggcctggg atttinttc ccctnttncc tccccccc ccnggganag aggttngngt
                                                                           660
tttgntcnnc ggccccnccn aaganctttn ccganttnan ttaaatccnt gcctnggcga
                                                                           720
agtccnttgn agggntaaan ggccccctnn cggg
                                                                           754
      <210> 21
       <211> 755
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(755)
      <223> n = A, T, C or G
atcancccat gaccccnaac nngggaccnc tcanccggnc nnncnaccnc cggccnatca
                                                                            60
nngtnagnnc actnonnttn natcacnocc encenactac gecenenane enacgeneta
                                                                           120
nncanatnce actganngcg cgangtngan ngagaaanct nataccanag ncaccanacn
                                                                           180
ccagctgtcc nanaangcct nnnatacngg nnnatccaat ntgnancctc cnaagtattn
                                                                           240
nnenneanat gatttteetn anecgattae centneecce tanecectee eccecaacna
                                                                           300
cgaaggenet ggneenaagg nngegnenee eegetagnte eeenneaagt eneneneeta
                                                                           360
aactcancen nattaenege ttentgagta teacteeceg aateteacee tacteaacte
                                                                           420
aaaaanatcn gatacaaaat aatncaagcc tgnttatnac actntgactg ggtctctatt
                                                                           480
ttagnggtcc ntnaanchtc ctaatacttc cagtctncct tcnccaattt ccnaanggct
                                                                           540
ctttcngaca gcatnttttg gttcccnntt gggttcttan ngaattgccc ttcntngaac
                                                                           600
gggctcntct tttccttcgg ttancctggn ttcnnccggc cagttattat ttcccntttt aaattcntnc cntttanttt tggcnttcna aacccccggc cttgaaaacg gccccctggt
                                                                           660
                                                                           720
aaaaggttgt tttganaaaa tttttgtttt gttcc
                                                                           755
      <210> 22
      <211> 849
      <212> DNA
```

```
<213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (849)
      <223> n = A, T, C \text{ or } G
      <400> 22
tttttttttt tttttangtg tngtcgtgca ggtagaggct tactacaant gtgaanacgt
acgctnggan taangcgacc cganttctag gannencect aaaatcanac tgtgaagatn
                                                                        120
                                                                        180
atcctgnnna cggaanggtc accggnngat nntgctaggg tgnccnctcc cannnenttn
cataacteng nggccetgee caccacette ggeggeeeng ngneegggee egggteattn
                                                                        240
gnnttaacen cactnique neggttteen neccenneng accenggega teeggggtne
                                                                        300
                                                                        360
tetgtettee cetgnagnen anaaantggg ceneggneee etttaceeet nnacaageea
engeenteta neenengeee eeetteeant nngggggaet geenannget eegttnetng
                                                                        420
nnacceennn gggtneeteg gttgtegant enacegnang ceanggatte enaaggaagg
                                                                        480
tgcgttnttg gcccctaccc ttcgctncgg nncacccttc ccgacnanga nccgctcccg
                                                                        540
chennequing ceteneeteq caacaceege netentengt neggninece ecceaecege
                                                                        600
necetenene ngnegnanen eteeneenee gteteannea ecaceegee eegeeaggee
                                                                        660
ntcanccaen ggnngaenng nagenennte geneegegen gegneneeet egeenengaa
                                                                        720
ctncntcnqq ccantnncqc tcaanconna cnaaacqccq ctqcqcqqcc cqnaqcqncc
                                                                        780
                                                                        840
ncctcenega gtecteegn etteenacee anguntteen egaggacaen nnaceeegee
                                                                        849
nncangcgg
      <210> 23
      <211> 872
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (872)
      <223> n = A, T, C or G
      <400> 23
gcgcaaacta tacttcgctc gnactcgtgc gcctcgctnc tcttttcctc cgcaaccatg
                                                                         60
totgacnano cogattnggo ngatatonan aagntogano agtocaaact gantaacaca
                                                                        120
cacacnenan aganaaatee netgeettee anagtanaen attgaaenng agaaecange
                                                                        180
nggcgaatcg taatnaggcg tgcgccgcca atntgtcncc gtttattntn ccagcntenc
                                                                        240
ctnccnaccc tacntcttcn nagctqtcnn acccctnqtn cqnacccccc naggtcggga
                                                                        300
tegggtttnn nntgacegng ennecette eccentecat nacganeene eegeaceaee
                                                                        360
nanngenege necegninet ettegeenee etgteetnin eeeetginge etggenengn
                                                                        420
accgcattga ccctcgccnn ctncnngaaa ncgnanacgt ccgggttgnn annancgctg
                                                                        480
tgggnnngcg tctgcnccgc gttccttccn ncnncttcca ccatcttcnt tacngggtct
                                                                        540
conceente tennneaene cetaggacge threethige coccettnae teccecett
                                                                        600
                                                                        660
cgncgtgncc cgnccccacc ntcatttnca nacgntcttc acaannncct ggntnnctcc
cnancngncn gtcanccnag ggaagggngg ggnnccnntg nttgacgttg nggngangtc
                                                                        720
cgaanantcc tencentean enctaceeet egggegnnet etengttnee aaettaneaa
                                                                        780
nteteccecy ngngemente teageetene concecenet etetgeanty tnetetgete
                                                                        840
tnaccnntac gantnttcgn cnccctcttt cc
                                                                        872
      <210> 24
      <211> 815
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (815)
      <223> n = A, T, C or G
      <400> 24
```

```
gcatgcaagc ttgagtattc tatagngtca cctaaatanc ttggcntaat catggtcnta
                                                                         .60
 nctgncttcc tgtgtcaaat gtatacnaan tanatatgaa tctnatntga caaganngta
                                                                        120
 tentneatta gtaacaantg tnntgteeat eetgtengan canatteeca tnnattnegn
                                                                        180
 cgcattenen geneantatn taatngggaa ntennntnnn neacenneat etatentnee
                                                                        240
 geneectgae tggnagagat ggatnantte tnntntgace nacatgttea tettggattn
                                                                        300
 aananceece egengneeae eggttngnng enageennte ecaagacete etgtggaggt
                                                                        360
 aacctgcgtc aganncatca aacntgggaa acccgcnncc angtnnaagt ngnnncanan
                                                                        420
 gatecegtee aggnttnace atceettene agegeeecet tingtgeett anagngnage
                                                                        480
 gtgtccnanc enctcaacat ganacgegee agneeanceg caattnggea caatgtegne
                                                                        540
 gaacccccta gggggantna thcaaanccc caggattgtc chchcangaa atccchcanc
                                                                        600
 ecencectae cennetttgg gaengtgaee aanteeegga gtneeagtee ggeengnete
                                                                        660
 ccccaccggt nnccntgggg gggtgaanct cngnntcanc cngncgaggn ntcgnaagga
                                                                        720
 accggneetn ggnegaanng anenntenga agngeenent egtataacce ecceteneca
                                                                        780
nccnacngnt agntccccc cngggtncgg aangg
                                                                        815
      <210> 25
      <211> 775
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(775)
      <223> n = A, T, C or G
      <400> 25
ccgagatgtc tcgctccgtg gccttagctg tgctcgcgct actctctt tctggcctgg
                                                                        60
aggetateca gegtaeteca aagatteagg titaeteaeg teatecagea gagaatggaa
                                                                       120
agtcaaattt cctgaattgc tatgtgtctg ggtttcatcc atccgacatt gaanttgact
                                                                       180
tactgaagaa tgganagaga attgaaaaag tggagcattc agacttgtct ttcagcaagg
                                                                       240
actggtcttt ctatctcntg tactacactg aattcacccc cactgaaaaa gatgagtatg
                                                                       300
cctgccgtgt gaaccatgtg actttgtcac agcccaagat agttaagtgg gatcgagaca
                                                                       360
tgtaagcagn cnncatggaa gtttgaagat gccgcatttg gattggatga attccaaatt
                                                                       420
ctgcttgctt gcnttttaat antgatatgc ntatacaccc taccctttat gnccccaaat
                                                                       480
tgtaggggtt acatnantgt tenentngga catgatette etttataant cencentteg
                                                                       540
aattgecegt enceengttn ngaatgttte ennaaceaeg gttggeteee eeaggtenee
                                                                       600
tettaeggaa gggeetggge enetttneaa ggttggggga acenaaaatt tenettntge
                                                                       660
concocneca enntettgng nneneanttt ggaaccette enatteecet tggeetenna
                                                                       720
nccttnncta anaaaacttn aaancgtngc naaanntttn acttcccccc ttacc
                                                                       775
      <210> 26
      <211> 820
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(820)
      <223> n = A, T, C or G
      <400> 26
anattantac agtgtaatct tttcccagag gtgtgtanag ggaacggggc ctagaggcat
                                                                        60
cccanagata nettatanca acagtgettt gaccaagage tgetgggeae attteetgea
                                                                       120
gaaaaggtgg cggtccccat cactcctcct ctcccatagc catcccagag gggtgagtag
                                                                       180
ccatcangcc ttcggtggga gggagtcang gaaacaacan accacagagc anacagacca
                                                                       240
ntgatgacca tgggcgggag cgagcetett ecetgnaccg gggtggcana nganagceta
                                                                       300
nctgaggggt cacactataa acgttaacga ccnagatnan cacctgcttc aagtgcaccc
                                                                       360
ttectacetg acnaecagng acennnaact gengeetggg gacagenetg ggancageta
                                                                       420
acnnageact cacetgeece eccatggeeg thegenteec tggteetgne aagggaaget
                                                                       480
ccctgttgga attncgggga naccaaggga nccccctcct ccanctgtga aggaaaaann
                                                                       540
gatggaattt thecetteeg geennteece tetteettta eaegeecet nntactente
                                                                       600
tecetetntt nteetgnene aettttnace cennnattte eettnattga teggannetn
                                                                       660
```

```
720
 qanattccac tnncgcctnc cntcnatcng naanacnaaa nactntctna cccnggggat
 gggnncctcg ntcatcctct ctttttcnct accnccnntt ctttgcctct ccttngatca
780tccaacente gntggeentn ecceecennn teetttneee
820
       <210> 27
       <211> 818
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(818)
       <223> n = A, T, C or G
       <400> 27
 tctgggtgat ggcctcttcc tcctcaggga cctctgactg ctctgggcca aagaatctct
                                                                           60
                                                                          120
 tqtttcttct ccqaqcccca ggcagcggtg attcagccct gcccaacctg attctgatga
 ctgcggatgc tgtgacggac ccaaggggca aatagggtcc cagggtccag ggaggggcgc
                                                                          180
 ctgctgagca cttccgcccc tcaccctgcc cagcccctgc catgagctct gggctgggtc
                                                                          240
                                                                          300
 tecqueteca gggttetget ettecangea ngecancaag tggegetggg ceacactgge
 ttetteetge ecentecetg getetgante tetgtettee tgteetgtge angeneettg
                                                                          360
                                                                          420
 gatctcaqtt tecetenete anngaactet gtttetgann tetteantta actntgantt
 tatnaccnan tggnctgtnc tgtcnnactt taatgggccn gaccggctaa tccctccctc
                                                                          480
 netceettee anttennnna accngettne ententetee centaneeeg cengggaane
                                                                          540
 ctcctttgcc ctnaccangg gccnnnaccg cccntnnctn ggggggcnng gtnnctncnc ctgntnnccc cnctcncnnt tncctcgtcc cnncnncgcn nngcannttc ncngtcccnn
                                                                          600
                                                                          660
 tnnetetten ngtntegnaa ngntenentn tnnnnngnen ngntnntnen teeetetene
                                                                          720
                                                                          780
 conntgnang tonttonnoc nengoneece nonnennon nggonotonn tetnenenge
 cccnncccc ngnattaagg cctccnntct ccggccnc
                                                                          818
       <210> 28
       <211> 731
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1) ... (731)
       <223> n = A, T, C or G
       <400> 28
 aggaagggcg gagggatatt gtangggatt gagggatagg agnataangg gggaggtgtg
 tcccaacatg anggtgnngt tctcttttga angagggttg ngtttttann ccnggtgggt
                                                                          120
                                                                          180
 qattnaaccc cattqtatqq aqnnaaaqqn tttnagggat ttttcggctc ttatcagtat
 ntanatteet gtnaategga aaatnatntt tennenggaa aatnttgete eeateegnaa
                                                                          240
 attnctcccg ggtagtgcat nttngggggn cngccangtt tcccaggctg ctanaatcgt
                                                                          300
 actaaagntt naagtgggan tncaaatgaa aacctnncac agagnatccn tacccgactg
                                                                          360
                                                                          420
 tnnnttncct tegecetntg actetgenng ageceaatac cenngngnat gtenecengn
                                                                          480
 nnnqcqncnc tqaaannnnc tcqnqqctnn qancatcang gggtttcgca tcaaaagcnn
 cgtttcncat naaggcactt tngcctcatc caaccnctng ccctcnncca tttngccgtc
                                                                          540
                                                                          600
 nggttenect acgetnntng encetnnntn ganattttne eegeetnggg naanceteet
                                                                          660
 gnaatgggta gggncttntc ttttnaccnn gnggtntact aatennetne acgentnett
                                                                           720
 totonaccco coccetttt caatoccane ggenaatggg gtotocconn cgangggggg
 nnncccannc c
                                                                          731
       <210> 29
       <211> 822
       <212> DNA
       <213> Homo sapien
       <220>
```

```
<221> misc feature
       <222> (1) ... (822)
       <223> n = A, T, C or G
       <400> 29
 actagtccag tgtggtggaa ttccattgtg ttggggncnc ttctatgant antnttagat
                                                                           60
cgctcanacc tcacancctc conacnangc ctataangaa nannaataga nctgtncnnt
                                                                          120
 atnintacne teatanneet ennnaceeae teeetettaa eeentaetgi geetaingen
                                                                          180
tnnctantct ntgccgcctn cnanccaccn gtgggccnac cncnngnatt ctcnatctcc
                                                                          240
tenecatntn gectananta ngtneatace etatacetae necaatgeta nnnetaanen
                                                                          300
tocatnantt annntaacta ccactgacnt ngactttonc atnanctoct aatttgaatc
                                                                          360
tactctgact cccacngcct annnattagc ancntccccc nacnatntct caaccaaatc
                                                                          420
ntcaacaacc tatctanctg ttcnccaacc nttncctccg atccccnnac aaccccctc
                                                                          480
ccaaataccc nccacctgac ncctaacccn caccatcccg gcaagccnan ggncatttan
                                                                          540
ccactggaat cacnatngga naaaaaaaac ccnaactctc tancncnnat ctccctaana
                                                                          600
aatnotootn naatttactn noantnocat caanoocacn tgaaacnnaa cocctgtttt
                                                                          660
tanatccctt ctttcgaaaa ccnacccttt annncccaac ctttngggcc cccccnctnc
                                                                          720
ccnaatgaaq gncncccaat cnangaaacg nccntgaaaa ancnaggcna anannntccg
                                                                          780
canatectat ecettanttn ggggneeett neeengggee ee
                                                                          822
       <210> 30
       <211> 787
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (787)
      <223> n = A, T, C or G
      <400> 30
cggccgcctg ctctggcaca tgcctcctga atggcatcaa aagtgatgga ctgcccattg
                                                                          60
ctagagaaga cettetetee tactgteatt atggageeet geagactgag ggeteeeett
                                                                         120
gtctgcagga tttgatgtct gaagtcgtgg agtgtqqctt qqaqctcctc atctacatna
                                                                         180
gctggaagcc ctggagggcc tctctcgcca gcctcccct tctctccacg ctctccangg
acaccagggg ctccaggcag cccattattc ccagnangac atggtgtttc tccacgcgga
                                                                         300
cccatggggc ctgnaaggcc agggtctcct ttgacaccat ctctcccgtc ctgcctggca
                                                                         360
ggccgtggga tccactantt ctanaacggn cgccaccncg gtgggagctc cagctttgt
                                                                         420
tecenttaat gaaggttaat tgenegettg gegtaateat nggteanaac tnttteetgt
                                                                         480
gtgaaattgt ttntcccctc ncnattccnc ncnacatacn aacccggaan cataaagtgt
                                                                         540
taaagcctgg gggtngcctn nngaatnaac tnaactcaat taattgcgtt ggctcatggc
                                                                         600
ccgctttccn ttcnggaaaa ctgtcntccc ctgcnttnnt gaatcggcca cccccngggaaaaagcggtt tgcnttttng ggggntcctt ccncttcccc cctcnctaan ccctncgcct
                                                                         660
                                                                         720
cggtcgttnc nggtngcggg gaangggnat nnnctcccnc naagggggng agnnngntat
                                                                         780
ccccaaa
                                                                         787
      <210> 31
      <211> 799
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(799)
      <223> n = A, T, C or G
      <400> 31
ttttttttt ttttttggc gatgctactg tttaattgca ggaggtgggg gtgtgtgtac
catgtaccag ggctattaga agcaagaagg aaggagggag ggcagagcgc cctgctgagc
                                                                         120
aacaaaggac teetgeagee ttetetgtet gtetettgge geaggeacat ggggaggeet
                                                                         180
cccgcagggt gggggccacc agtccagggg tgggagcact acanggggtg ggagtgggtg
                                                                         240
gtggctggtn cnaatggcct gncacanatc cctacgattc ttgacacctg gatttcacca
                                                                         300
```

```
360
qqqqaccttc tqttctccca nqqnaacttc ntnnatctcn aaagaacaca actgtttctt
                                                                       420
engeanttet ggetgtteat ggaaageaca ggtgteenat tinggetggg aettggtaca
tatqqttccq qcccacctct ccentenaan aagtaattca ccccccccn centctnttg
                                                                       480
cctgggccct taantaccca caccggaact canttantta ttcatcttng gntgggcttg
                                                                       540
                                                                       600
ntnatcheen eetgaangeg eeaagttgaa aggeeaegee gtheeenete eecatagnan
nttttnncnt canctaatge ecceeengge aacnateeaa teeceeecen tgggggeeee
                                                                       660
ageceangge eccegneteg ggnnneengn enegnantee ecaggntete ceantengne
                                                                       720
                                                                       780
connigence eccquacqua quacanaaqq ntngaqeene egcanninnin nggtinenae
                                                                       799
ctcgccccc ccnncgnng
      <210> 32
      <211> 789
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (789)
      <223> n = A, T, C or G
      <400> 32
                                                                        60
tttttttt tttttttt tttttttt
ttttnccnag ggcaggttta ttgacaacct cncgggacac aancaggctg gggacaggac
                                                                        120
ggcaacaggc tccggcggcg gcggcggcgg ccctacctgc ggtaccaaat ntgcagcctc cgctcccgct tgatnttcct ctgcagctgc aggatgccnt aaaacagggc ctcggccntn
                                                                       180
                                                                       240
                                                                        300
ggtgggcacc ctgggatttn aatttccacg ggcacaatgc ggtcgcancc cctcaccacc
nattaggaat agtggtntta cccncenceg ttggcncact ccccntggaa accacttntc
                                                                       360
                                                                        420
geggeteegg catetggtet taaacettge aaacnetggg geeetetttt tggttantnt
                                                                        480
ncengecaca atcatnacte agactggene gggetggece caaaaaanen eeccaaaace
ggnccatgtc ttnncggggt tgctgcnatn tncatcacct cccgggcnca ncaggncaac
                                                                       540
ccaaaagttc ttgnggcccn caaaaaanct ccggggggnc ccagtttcaa caaagtcatc
                                                                        600
ccccttqqcc cccaaatcct cccccqntt nctgggtttg ggaacccacg cctctnnctt
                                                                        660
                                                                        720
tggnnggcaa gntggntccc ccttcgggcc cccggtgggc ccnnctctaa ngaaaacncc
ntectnnnca ceateceee nngnnaegne tancaangna teeettttt tanaaaeggg
                                                                        780
                                                                        789
cccccncq
      <210> 33
      <211> 793
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(793)
      <223> n = A, T, C or G
      <400> 33
qacaqaacat qttqqatqqt qqaqcacctt tctatacqac ttacaggaca gcagatgggg
                                                                         60
                                                                        120
aattcatggc tgttggagca atanaacccc agttctacga gctgctgatc aaaggacttg
qactaaaqtc tgatqaactt cccaatcaga tgagcatgga tgattggcca gaaatgaana
                                                                        180
                                                                        240
agaagtttgc agatgtattt gcaaagaaga cgaaggcaga gtggtgtcaa atctttgacg
                                                                        300
gcacagatgc ctgtgtgact ccggttctga cttttgagga ggttgttcat catgatcaca
                                                                        360
acaangaacg gggctcgttt atcaccantg aggagcagga cgtgagcccc cgccctgcac
ctctgctgtt aaacacccca gccatccctt ctttcaaaag ggatccacta cttctagagc
                                                                        420
                                                                        480
ggncqccacc gcggtggagc tccagctttt gttcccttta gtgagggtta attgcgcgct
                                                                        540
tggcgtaatc atggtcatan ctgtttcctg tgtgaaattg ttatccgctc acaattccac
acaacatacg anccggaagc atnaaatttt aaagcctggn ggtngcctaa tgantgaact
                                                                        600
nactcacatt aattggcttt gegeteactg ecegettice agteeggaaa acetgieett
                                                                        660
gccagctgcc nttaatgaat enggccaccc cccggggaaa aggcngtttg cttnttgggg
                                                                        720
                                                                        780
egenetteee getttetege tteetgaant eetteeeee ggtetttegg ettgeggena
                                                                        793
acggtatcna cct
```

```
<210> 34
       <211> 756
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (756)
       <223> n = A,T,C or G
       <400> 34
 gccgcgaccg gcatgtacga gcaactcaag ggcgagtgga accgtaaaag ccccaatctt
                                                                           60
 ancaagtgcg gggaanagct gggtcgactc aagctagttc ttctggagct caacttcttg
                                                                          120
ccaaccacag ggaccaagct gaccaaacag cagctaattc tggcccgtga catactggag
                                                                          180
atcggggccc aatggagcat cctacgcaan gacatcccct ccttcgagcg ctacatggcc
                                                                          240
cageteaaat getaetaett tgattacaan gageagetee eegagteage etatatgeae
                                                                          300
cagetettgg geeteaacet eetetteetg etgteecaga aeegggtgge tgantnecae
                                                                          360
acgganttgg ancggctgcc tgcccaanga catacanacc aatgtctaca tcnaccacca
                                                                          420
gtgtcctgga gcaatactga tgganggcag ctaccncaaa gtnttcctgg ccnagggtaa
                                                                          480
catececege egagagetae acettettea ttgacateet getegacaet atcagggatg
                                                                          540
aaaatcgcng ggttgctcca gaaaggctnc aanaanatcc ttttcnctga aggcccccgg
                                                                          600
athenetagt netagaateg geoegecate geggtggane etceaacett tegttheeet ttaetgaggg ttnattgeeg eeettggegt tateatggte aeneengttn eetgtgtga
                                                                          660
                                                                          720
aattnttaac ccccacaat tccacgccna cattng
                                                                          756
      <210> 35
      <211> 834
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (834)
      <223> n = A, T, C or G
      <400> 35
ggggatetet anatenacet gnatgeatgg ttgteggtgt ggtegetgte gatgaanatg
                                                                           60
aacaggatet tgecettgaa getetegget getgtnttta agttgeteag tetgeegtea
                                                                          120
tagtcagaca cnctcttggg caaaaaacan caggatntga gtcttgattt cacctccaat
                                                                          180
aatettengg getgtetget eggtgaacte gatgaenang ggeagetggt tgtgtntgat
                                                                          240
aaantccanc angttctcct tggtgacctc cccttcaaag ttgttccggc cttcatcaaa
                                                                          300
cttctnnaan angannancc canctttgtc gagctggnat ttgganaaca cgtcactgtt
                                                                          360
ggaaactgat cccaaatggt atgtcatcca tcgcctctgc tgcctgcaaa aaacttgctt
                                                                          420
ggeneaaate egacteecen teettgaaag aageenatea cacceccete eetggactee
                                                                          480
nncaangact ctnccgctnc cccntccnng cagggttggt ggcannccgg gcccntgcgc
                                                                         540
ttcttcagcc agttcacnat nttcatcagc ccctctgcca gctgttntat tccttggggg
                                                                          600
ggaancegte tetecettee tgaannaact ttgaccgtng gaatageege genteneent
                                                                          660
acninctggg ccgggttcaa anteceteen tignennien cetegggeca tietggatti
                                                                         720
ncenaacttt tteetteece eneceenegg ngtttggntt ttteatnggg ecceaactet
                                                                         780
getnttggcc anteceetgg gggentntan enceeetnt ggtccentng ggcc
                                                                         834
      <210> 36
      <211> 814
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(814)
      <223> n = A, T, C or G
      <400> 36
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```
cggncgcttt ccngccgcgc cccqtttcca tgacnaaggc tcccttcang ttaaatacnn
                                                                         60
 cctagnaaac attaatgggt tgctctacta atacatcata cnaaccagta agcctgccca
                                                                        120
                                                                        180
 naacgccaac tcaggccatt cctaccaaag gaagaaaggc tggtctctcc accccctgta
                                                                        240
 ggaaaggeet geettgtaag acaccacaat neggetgaat etnaagtett gtgttttaet
                                                                        300
 aatggaaaaa aaaaataaac aanaggtttt gttctcatgg ctgcccaccg cagcctggca
 ctaaaacanc ccagcgctca cttctgcttg ganaaatatt ctttgctctt ttggacatca
                                                                        360
 ggettgatgg tatcactgcc acntttccac ccagctgggc ncccttcccc catntttgtc
                                                                        420
 antganctgg aaggeetgaa nettagtete caaaagtete ngeecacaag aceggeeace
                                                                        480
 aggggangtc ntttncagtg gatctgccaa anantacccn tatcatcnnt gaataaaaag
                                                                        540
                                                                        600
 qcccctqaac qanatqcttc cancancctt taagacccat aatcctngaa ccatggtgcc
 cttccggtct gatccnaaag gaatgttcct gggtcccant ccctcctttg ttncttacgt
                                                                        660
 tgtnttggac contgctngn atnacccaan tganatcccc ngaagcaccc tncccctggc
                                                                        720
                                                                        780
 atttganttt entaaattet etgeeetaen netgaaagea enatteeetn ggeneenaan
                                                                        814
 ggnqaactca agaaggtctn ngaaaaacca cncn
       <210> 37
       <211> 760
       <212> DNA
       <213> Homo sapien
       <221> misc feature
       <222> (1)...(760)
       <223> n = A, T, C or G
       <400> 37
                                                                         60
. qcatqctqct cttcctcaaa qttqttcttq ttgccataac aaccaccata ggtaaagcgg
 gcgcagtgtt cgctgaaggg gttgtagtac cagcgcggga tgctctcctt gcagagtcct
                                                                         120
                                                                        180
 gtgtctggca ggtccacgca atgccctttg tcactgggga aatggatgcg ctggagctcg
                                                                        240
 tenaaneeae tegtgtattt tteacangea geeteeteeg aagenteegg geagttgggg
 gtgtcgtcac actccactaa actgtcgatn cancagccca ttgctgcagc ggaactgggt
                                                                         300
                                                                         360
 gggctgacag gtgccagaac acactggatn ggcctttcca tggaagggcc tgggggaaat
                                                                         420
 cncctnance caaactgcct ctcaaaggcc accttgcaca ccccgacagg ctagaaatgc
 actottotto ccaaaggtag ttgttottgt tgcccaagca ncctccanca aaccaaaanc
                                                                         480
                                                                        540
 ttgcaaaatc tgctccgtgg gggtcatnnn taccanggtt ggggaaanaa acccggcngn
 qancenectt qtttqaatqc naaqqnaata atectectgt cttgettggg tggaanagca
                                                                         600
                                                                         660
 caattgaact gttaachttg ggccgngttc chctngggtg gtctgaaact aatcaccgtc
                                                                         720
 actggaaaaa ggtangtgcc ttccttgaat tcccaaantt cccctngntt tgggtnnttt
                                                                         760
 ctcctctncc ctaaaaatcg tnttcccccc ccntanggcg
       <210> 38
       <211> 724
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1)...(724)
       <223> n = A, T, C or G
       <400> 38
 ttttttttt tttttttt tttttttt tttttaaaaa ccccctccat tgaatgaaaa
                                                                         120
 cttccnaaat tqtccaaccc cctcnnccaa atnnccattt ccgggggggg gttccaaacc
                                                                         180
 caaattaatt ttgganttta aattaaatnt tnattngggg aanaanccaa atgtnaagaa
 aatttaaccc attatnaact taaatnootn gaaacccntg gnttocaaaa atttttaacc
                                                                         240
 cttaaatccc tccgaaattg ntaanggaaa accaaattcn cctaaggctn tttgaaggtt
                                                                         300
 ngatttaaac ccccttnant tnttttnacc cnngnctnaa ntatttngnt tccggtgttt
                                                                         360
                                                                         420
 tectnttaan entnggtaac teeegntaat gaannneett aanceaatta aacegaattt
                                                                         480
 tttttqaatt qqaaattccn nqqqaattna ccqqqqtttt tcccntttgg gggccatncc
                                                                         540
 cccnctttcg gggtttgggn ntaggttgaa ttttnnang ncccaaaaaa ncccccaana
 aaaaaactcc caagnnttaa ttngaatntc ccccttccca ggccttttgg gaaaggnggg
                                                                         600
                                                                         660
 tttntggggg cengggantt entteeceen ttneeneece eeceenggt aaanggttat
```

```
ngnntttggt ttttgggccc cttnanggac cttccggatn gaaattaaat ccccgggncg
                                                                        720
 gccg
                                                                        724
       <210> 39
       <211> 751
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
       <222> (1) ... (751)
       <223> n = A, T, C or G
      <400> 39
ttttttttt tttttttt ctcacattta atttttattt tgatttttt taatgctgca
                                                                         60
caacacaata tttatttcat ttgtttcttt tatttcattt tatttgtttg ctgctgct
                                                                        120
tttatttatt tttactgaaa gtgagaggga acttttgtgg cctttttcc ttttctgta
                                                                        180
ggccgcctta agctttctaa atttggaaca tctaagcaag ctgaanggaa aagggggttt
                                                                       240
cgcaaaatca ctcgggggaa nggaaaggtt gctttgttaa tcatgcccta tggtgggtga
                                                                       300
ttaactgctt gtacaattac ntttcacttt taattaattg tgctnaangc tttaattana
                                                                       360
cttgggggtt ccctccccan accaacccn ctgacaaaaa gtgccngccc tcaaatnatg
                                                                       420
teceggennt entigaaaca caengengaa ngtteteatt nteecenene cagginaaaa
                                                                       480
tgaagggtta ccatntttaa cnccacctcc acntggcnnn gcctgaatcc tcnaaaanen
                                                                       540
ccctcaanch aattnotning ccccggtone gentingtee eneccggget eegggaantn
                                                                       600
caccecenga annenntnne naacnaaatt eegaaaatat teeenntene teaatteeee
                                                                       660
cnnagactnt cetennenan encaatttte ttttnntcac gaacnegnne ennaaatgn
                                                                       720
nnnncncctc cnctngtccn naatcnccan c
                                                                       751
      <210> 40
      <211> 753
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(753)
      <223> n = A, T, C or G
      <400> 40
gtggtatttt ctgtaagatc aggtgttcct ccctcgtagg tttagaggaa acaccctcat
                                                                        60
agatgaaaac ccccccgaga cagcagcact gcaactgcca agcagccggg qtaggagggg
                                                                       120
cgccctatgc acagctgggc ccttgagaca gcagggcttc gatgtcaggc tcgatgtcaa
                                                                       180
tggtctggaa gcggcggctg tacctgcgta ggggcacacc gtcagggccc accaggaact
                                                                       240
tctcaaagtt ccaggcaacn tcgttgcgac acaccggaga ccaggtgatn agcttggggt
                                                                       300
cggtcataan cgcggtggcg tcgtcgctgg gagctggcag ggcctcccgc aggaaggcna
                                                                       360
ataaaaggtg cgccccgca ccgttcanct cgcacttctc naanaccatg angttgggct
                                                                       420
cnaacccacc accanneegg actteettga nggaatteec aaatetette gntettggge
                                                                       480
ttctnctgat gccctanctg gttgcccngn atgccaanca nccccaance ccggggtcct
                                                                       540
aaancaccon cotcotontt toatotgggt tnttntcccc ggaccntggt tootctcaag
                                                                       600
ggancccata tctcnaccan tactcaccnt ncccccccnt gnnacccanc cttctanngn
                                                                       660
ttcccncccg ncctctggcc cntcaaanan gcttncacna cctgggtctg ccttccccc
                                                                       720
tnccctatct gnaccccncn tttgtctcan tnt
                                                                       753
      <210> 41
      <211> 341
      <212> DNA
      <213> Homo sapien
      <400> 41
actatatcca tcacaacaga catgcttcat cccatagact tcttgacata gcttcaaatg
                                                                        60
agtgaaccca tccttgattt atatacatat atgttctcag tattttggga gcctttccac
                                                                       120
ttctttaaac cttgttcatt atgaacactg aaaataggaa tttgtgaaga gttaaaaagt
                                                                       180
```

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tatagettgt ttaegtagta agtttttgaa g tgttaaactg tgatttttaa aaaatateat t ttttaetttt tgattaattg tgttttatat a	ttgagaatat	tctttcagag		240 300 341
<210> 42 <211> 101 <212> DNA <213> Homo sapien				
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<210> 43 <211> 305 <212> DNA <213> Homo sapien				
<400> 43				
acatctttgt tacagtctaa gatgtgttct t tccagggtgg tctcacactg taattagage t tcagatgcct tgctaagtct agagttctag a cctcttgaga ggtcagtaaa gaggacttaa t tggatacaga acgagagtta tcctggataa c	tattgaggag agttatgttt tatttcatat	tctttacagc cagaaagtct ctacaaaatg	aaattaagat aagaaaccca accacaggat	60 120 180 240 300 305
<210> 44 <211> 852 <212> DNA <213> Homo sapien			·	
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<210> 45 <211> 234 <212> DNA <213> Homo sapien				
<400> 45				~~
acaacagacc cttgctcgct aacgacctca f agtctgacac catccggagc atcagcattg o gcctcgtttc tggctggggt ctgctggcga a	cttcgcagtg	ccctaccgcg	gggaactctt	60 120 180

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tgaacgtgtc ggtggtgtct gaggaggtct gcagtaagct ctatgacccg ctgt
                                                                       234
      <210> 46
       <211> 590
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(590)
      <223> n = A, T, C or G
      <400> 46
actttttatt taaatgttta taaggcagat ctatgagaat gatagaaaac atggtgtgta
atttgatagc aatattttgg agattacaga gttttagtaa ttaccaatta cacagttaaa
                                                                       120
aagaagataa tatattocaa goanatacaa aatatotaat gaaagatoaa ggoaggaaaa
                                                                       180
tgantataac taattgacaa tggaaaatca attttaatgt gaattgcaca ttatccttta
                                                                       240
aaagctttca aaanaaanaa ttattgcagt ctanttaatt caaacagtgt taaatggtat
                                                                       300
caggataaan aactgaaggg canaaagaat taattttcac ttcatgtaac ncacccanat
                                                                       360
ttacaatggc ttaaatgcan ggaaaaagca gtggaagtag ggaagtantc aaggtctttc
                                                                       420
tggtctctaa tctgccttac tctttgggtg tggctttgat cctctggaga cagctgccag
                                                                       480
ggctcctgtt atatccacaa tcccagcagc aagatgaagg gatgaaaaag gacacatgct
                                                                       540
gccttccttt gaggagactt catctcactg gccaacactc agtcacatgt
                                                                       590
      <210> 47
      <211> 774
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(774)
      <223> n = A,T,C or G
      <400> 47
acaagggggc ataatgaagg agtggggana gattttaaag aaggaaaaaa aacgaggccc
tgaacagaat tttcctgnac aacggggctt caaaataatt ttcttgggga ggttcaagac
                                                                       120
gcttcactgc ttgaaactta aatggatgtg ggacanaatt ttctgtaatg accctgaggg
                                                                       180
cattacagac gggactctgg gaggaaggat aaacagaaag gggacaaagg ctaatcccaa
                                                                       240
aacatcaaag aaaggaaggt ggcgtcatac ctcccagcct acacagttct ccagggctct
                                                                       300
ceteatecet ggaggaegae agtggaggaa caactgaeca tgteeceagg eteetgtgtg
                                                                       360
ctggctcctg gtcttcagcc cccagctctg gaagcccacc ctctgctgat cctgcgtggc
                                                                       420
ccacacteet tgaacacaca tecceaggtt atatteetgg acatggetga aceteetatt
                                                                       480
cctacttccg agatgccttg ctccctgcag cctgtcaaaa tcccactcac cctccaaacc
                                                                       540
acggcatggg aagcctttct gacttgcctg attactccag catcttggaa caatccctga
                                                                       600
ttccccactc cttagaggca agatagggtg gttaagagta gggctggacc acttggagcc
                                                                       660
aggetgetgg etteaaattn tggeteattt aegagetatg ggaeettggg eaagtnatet
                                                                       720
tcacttctat gggcntcatt ttgttctacc tgcaaaatgg gggataataa tagt
                                                                       774
      <210> 48
      <211> 124
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (124)
      <223> n = A, T, C or G
      <400> 48
canaaattga aattttataa aaaggcattt ttctcttata tccataaaat gatataattt
                                                                        60
ttgcaantat anaaatgtgt cataaattat aatgttcctt aattacagct caacgcaact
                                                                       120
```

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tggt
                                                                        124
      <210> 49
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (147)
      <223> n = A, T, C or G
      <400> 49
gccgatgcta ctattttatt gcaggaggtg ggggtgtttt tattattctc tcaacaqctt
tgtggctaca ggtggtgtct gactgcatna aaaantiitt tacgggtgat tgcaaaaatt
                                                                        120
ttagggcacc catatcccaa gcantgt
                                                                        147
      <210> 50
      <211> 107
      <212> DNA
      <213> Homo sapien
acattaaatt aataaaagga ctgttggggt tctgctaaaa cacatggctt gatatattgc
                                                                         60
atggtttgag gttaggagga gttaggcata tgttttggga gaggggt
                                                                        107
      <210> 51
      <211> 204
      <212> DNA
      <213> Homo sapien
      <400> 51
gtcctaggaa gtctagggga cacacgactc tggggtcacg gggccgacac acttgcacgg
cgggaaggaa aggcagagaa gtgacaccgt cagggggaaa tgacagaaag gaaaatcaag
                                                                        120
gccttgcaag gtcagaaagg ggactcaggg cttccaccac agccctgccc cacttggcca
                                                                        180
cctccctttt gggaccagca atgt
                                                                        204
      <210> 52
      <211> 491
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(491)
      <223> n = A, T, C or G
      <400> 52
acaaaqataa catttatctt ataacaaaaa tttqataqtt ttaaaqqtta qtattqtqta
qqqtattttc caaaaqacta aaqaqataac tcaqqtaaaa aqttaqaaat qtataaaaca
                                                                        120
ccatcagaca ggtttttaaa aaacaacata ttacaaaatt agacaatcat ccttaaaaaa
                                                                        180
aaaacttctt gtatcaattt cttttgttca aaatgactga cttaantatt tttaaatatt
tcanaaacac ttcctcaaaa attttcaana tggtagcttt canatgtncc ctcagtccca
                                                                        300
atgttgctca gataaataaa tctcgtgaga acttaccacc caccacaagc tttctggggc
                                                                        360
atgcaacagt gtctttctt tnctttttct ttttttttt ttacaggcac agaaactcat
                                                                        420
caattttatt tggataacaa agggtctcca aattatattg aaaaataaat ccaagttaat
                                                                        480
atcactcttq t
                                                                        491
      <210> 53
      <211> 484
      <212> DNA
      <213> Homo sapien
```

<210> 58

```
<220>
       <221> misc_feature
       <222> (1) ... (484)
       <223> n = A, T, C or G
      <400> 53
acataattta gcagggctaa ttaccataag atgctattta ttaanaggtn tatgatctga
                                                                         60
 gtattaacag ttgctgaagt ttggtatttt tatgcagcat tttctttttg ctttgataac
                                                                        120
actacagaac ccttaaggac actgaaaatt agtaagtaaa gttcagaaac attagctgct
                                                                        180
caatcaaatc totacataac actatagtaa ttaaaacgtt aaaaaaaagt gttgaaatct
                                                                        240
gcactagtat anaccgctcc tgtcaggata anactgcttt ggaacagaaa gggaaaaanc
                                                                        300
agetttgant ttetttgtge tgatangagg aaaggetgaa ttacettgtt geeteteeet
                                                                        360
aatgattggc aggtenggta aatnecaaaa catattecaa etcaacaett etttteeneg
                                                                        420
tancttgant ctgtgtattc caggancagg cggatggaat gggccagccc ncggatgttc
                                                                        480
      <210> 54
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 54
actaaacctc gtgcttgtga actccataca gaaaacggtg ccatccctga acacggctgg
                                                                         .60
ccactgggta tactgctgac aaccgcaaca acaaaaacac aaatccttgg cactggctag
                                                                        120
tctatgtcct ctcaagtgcc tttttgtttg t
                                                                        151
      <210> 55
      <211> 91
      <212> DNA
      <213> Homo sapien
      <400> 55
acctggcttg tctccgggtg gttcccggcg cccccacgg tccccagaac ggacactttc
                                                                         60
gccctccagt ggatactcga gccaaagtgg t
                                                                         91
      <210> 56
      <211> 133
      <212> DNA
      <213> Homo sapien
      <400> 56
ggcggatgtg cgttggttat atacaaatat gtcattttat gtaagggact tqaqtatact
                                                                         60
tggatttttg gtatctgtgg gttgggggga cggtccagga accaataccc catggatacc
                                                                        120
aagggacaac tgt
                                                                        133
      <210> 57
      <211> 147
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(147)
      <223> n = A, T, C or G
      <400> 57
actotggaga acctgagoog otgotocgoo totgggatga ggtgatgcan gongtggogo
                                                                        60
gactgggagc tgagcccttc cctttgcgcc tgcctcagag gattgttgcc gacntgcana
                                                                       120
tctcantggg ctggatncat gcagggt
                                                                       147
```

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<211> 198
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (198)
       <223> n = A, T, C or G
       <400> 58
 acagggatat aggtttnaag ttattgtnat tgtaaaatac attgaatttt ctgtatactc
                                                                         60
 tgattacata catttatcct ttaaaaaaga tgtaaatctt aatttttatg ccatctatta
                                                                         120
 atttaccaat gagttacctt gtaaatgaga agtcatgata gcactgaatt ttaactagtt
                                                                         180
                                                                         198
 ttgacttcta agtttggt
       <210> 59
       <211> 330
       <212> DNA
       <213> Homo sapien
       <400> 59
 acaacaaatg ggttgtgagg aagtcttatc agcaaaactg gtgatggcta ctgaaaagat
                                                                          60
 ccattgaaaa ttatcattaa tgattttaaa tgacaagtta tcaaaaactc actcaatttt
                                                                         120
                                                                         180
 cacctgtgct agcttgctaa aatgggagtt aactctagag caaatatagt atcttctgaa
 tacagtcaat aaatgacaaa gccagggcct acaggtggtt tccagacttt ccagacccag
                                                                         240
 cagaaggaat ctatttatc acatggatct ccgtctgtgc tcaaaatacc taatgatatt
                                                                         300
. tttcgtcttt attggacttc tttgaagagt
                                                                         330
       <210> 60
       <211> 175
       <212> DNA
       <213> Homo sapien
       <400> 60
                                                                         60
 acceptgggtg cettetacat teefgacgge teetteacca acatetggtt etaettegge
                                                                         120
 qtcqtqqqct ccttcctctt catcctcatc cagctqqtqc tqctcatcqa ctttqcqcac
                                                                         175
 tectggaace ageggtgget gggcaaggee gaggagtgeg attecegtge etggt
       <210> 61
       <211> 154
       <212> DNA
       <213> Homo sapien
       <400> 61
                                                                         60
 accocacttt teeteetgtg ageagtetgg actteteact getacatgat gagggtgagt
 ggttgttgct cttcaacagt atcctcccct ttccggatct gctgagccgg acagcagtgc
                                                                         120
                                                                        154
 tggactgcac agccccgggg ctccacattg ctgt
       <210> 62
       <211> 30
       <212> DNA
       <213> Homo sapien
       <400> 62
                                                                         30
 cgctcgagcc ctatagtgag tcgtattaga
       <210> 63
       <211> 89
       <212> DNA
       <213> Homo sapien
       <400> 63
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acaagtcatt tcagcaccct ttgctcttca aaactgacca tcttttatat ttaatgcttc ctgtatgaat aaaaatggtt atgtcaagt	60 89
<210> 64 <211> 97 <212> DNA <213> Homo sapien	
<400> 64 accggagtaa ctgagtcggg acgctgaatc tgaatccacc aataaataaa ggttctgcag aatcagtgca tccaggattg gtccttggat ctggggt	60 97
<210> 65 <211> 377 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(377) <223> n = A,T,C or G	
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<210> 66 <211> 305 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 66 acgcctttcc ctcagaattc agggaagaga ctgtcgcctg ccttcctccg ttgttgcgtg agaacccgtg tgccccttcc caccatatcc accctcgctc catctttgaa ctcaaacacg aggaactaac tgcaccctgg tcctctcccc agtccccagt tcaccctcca tcctccactc taagggatat caacactgcc cagcacaggg gccctgaatt tatgtggttt ttatatattt tttaataaga tgcactttat gtcattttt aataaagtct gaagaattac tgttt</pre>	60 120 180 240 300 305
<210> 67 <211> 385 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 67 actacacaca ctccacttgc ccttgtgaga cactttgtcc cagcacttta ggaatgctga ggtcggacca gccacatctc atgtgcaaga ttgcccagca gacatcaggt ctgagagttc cccttttaaa aaaggggact tgcttaaaaa agaagtctag ccacgattgt gtagagcagc tgggcagtc tggagattca cttttgaggag agttctcctc tgagacctga tctttagagg ctgggcagtc ttgcacatga gatggggctg gtctgatctc agcactcctt agtctgctg cctctcccag ggccccagcc tggccacacc tgcttacagg gcactctcag atgcccatac catagtttct gtgctagtgg accgt</pre>	60 120 180 240 300 360 385
<210> 68 <211> 73 <212> DNA <213> Homo sapien	

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<400> 68
 acttaaccag atatatttt accccagatg gggatattct ttgtaaaaaa tgaaaataaa
                                                                         60
 gtttttttaa tgg
                                                                         73
       <210> 69
       <211> 536
       <212> DNA
       <213> Homo sapien
       <220>
      <221> misc feature
       <222> (1) ... (536)
      <223> n = A, T, C or G
      <400> 69
actagtccag tgtggtggaa ttccattgtg ttgggggctc tcaccctcct ctcctgcage
                                                                        60
tocagetttg tgetetgeet etgaggagae catggeecag catetgagta ecetgetget
                                                                        120
cctgctggcc accctagctg tggccctggc ctggagcccc aaggaggagg ataggataat
                                                                        180
cccgggtggc atctataacg cagacctcaa tgatgagtgg gtacagcgtg cccttcactt
                                                                        240
cgccatcagc gagtataaca aggccaccaa agatgactac tacagacgtc cgctgcgggt
                                                                       300
actaagagcc aggcaacaga ccgttggggg ggtgaattac ttcttcgacg tagaggtggg
                                                                       360
ccgaaccata tgtaccaagt cccagcccaa cttggacacc tgtgccttcc atgaacagcc
                                                                       420
agaactgcag aagaaacagt tgtgctcttt cgagatctac gaagttccct ggggagaaca
                                                                       480
gaangtccct gggtgaaatc caggtgtcaa gaaatcctan ggatctgttg ccaggc
                                                                       536
      <210> 70
      <211> 477
      <212> DNA
      <213> Homo sapien
atgaccecta acaggggee teteageest cetaatgace teeggeetag ceatgtgatt
                                                                        60
teactteeae tecataaege teeteataet aggeetaeta accaacaea taaccatata
                                                                       120
ccaatgatgg cgcgatgtaa cacgagaaag cacataccaa ggccaccaca caccacctgt
                                                                       180
ccaaaaaggc cttcgatacg ggataatcct atttattacc tcagaagttt ttttcttcgc
                                                                       240
agggattitt ctgagccttt taccactcca gcctagcccc taccccccaa ctaggagggc
                                                                       300
actggcccc aacaggcatc accccgctaa atcccctaga agtcccactc ctaaacacat
                                                                       360
ccgtattact cgcatcagga gtatcaatca cctgagctca ccatagtcta atagaaaaca
                                                                       420
accqaaacca aattattcaa agcactgctt attacaattt tactgggtct ctatttt
                                                                       477
      <210> 71
      <211> 533
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(533)
      <223> n = A,T,C or G
agagctatag gtacagtgtg atctcagctt tgcaaacaca ttttctacat agatagtact
                                                                        60
aggtattaat agatatgtaa agaaagaaat cacaccatta ataatggtaa gattggttta
                                                                       120
tgtgatttta gtggtatttt tggcaccctt atatatgttt tccaaacttt cagcagtgat
                                                                       180
attatttcca taacttaaaa agtgagtttg aaaaagaaaa tctccagcaa gcatctcatt
                                                                       240
taaataaagg tttgtcatct ttaaaaaatac agcaatatgt gactttttaa aaaagctgtc
                                                                       300
aaataggtgt gaccctacta ataattatta gaaatacatt taaaaacatc gagtacctca
                                                                       360
aqtcagtttq ccttgaaaaa tatcaaatat aactcttaga gaaatgtaca taaaagaatg
                                                                       420
cttcgtaatt ttggagtang aggttccctc ctcaattttq tatttttaaa aagtacatgg
                                                                       480
taaaaaaaaa aattcacaac agtatataag gctgtaaaat gaagaattct gcc
                                                                       533
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<211> 511
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(511)
      <223> n = A, T, C \text{ or } G
      <400> 72
                                                                       60
tattacggaa aaacacacca cataattcaa ctancaaaga anactgcttc agggcgtgta
aaatgaaagg cttccaggca gttatctgat taaagaacac taaaagaggg acaaggctaa
aagccgcagg atgtctacac tatancaggc gctatttggg ttggctggag gagctgtgga
                                                                      180
                                                                      240
aaacatggan agattggtgc tgganatcgc cgtggctatt cctcattgtt attacanagt
                                                                      300
gaggttctct gtgttgcccac tggtttgaaa accgttctnc aataatgata gaatagtaca
cacatgagaa ctgaaatggc ccaaacccag aaagaaagcc caactagatc ctcagaanac
                                                                      3.60
gcttctaggg acaataaccg atgaagaaaa gatggcctcc ttgtgccccc gtctgttatg
                                                                      420
atttctctcc attgcagcna naaacccgtt cttctaagca aacncaggtg atgatggcna
                                                                      480
                                                                      511
aaatacaccc cctcttgaag naccnggagg a
      <210> 73
      <211> 499
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (499)
      <223> n = A, T, C or G
      <400> 73
                                                                       60
cagtgccagc actggtgcca gtaccagtac caataacagt gccagtgcca gtgccagcac
cagtggtggc ttcagtgctg gtgccagcct gaccgccact ctcacatttg ggctcttcgc
                                                                      120
tggccttggt ggagctggtg ccagcaccag tggcagctct ggtgcctgtg gtttctccta
                                                                      180
caagtgagat tttagatatt gttaatcctg ccagtctttc tcttcaagcc agggtgcatc
                                                                      240
                                                                      300
ctcagaaacc tactcaacac agcactctag gcagccacta tcaatcaatt gaagttgaca
360
antitaqaqq gecegittaa accegetgat cageetegae tqtgeettet antitgecage
                                                                      420
catctgttgt ttgcccctcc cccgntgcct tccttgaccc tggaaagtgc cactcccact
                                                                      480
qtcctttcct aantaaaat
                                                                      499
      <210> 74
      <211> 537
      <212> DNA
      <213> Homo sapien
      <220>
     <221> misc_feature
      <222> (1)...(537)
      <223> n = A, T, C \text{ or } G
      <400> 74
                                                                       60
tttcatagga gaacacactg aggagatact tgaagaattt ggattcagcc gcgaagagat
                                                                      120
ttatcagctt aactcagata aaatcattga aagtaataag gtaaaagcta gtctctaact
tccaggccca cggctcaagt gaatttgaat actgcattta cagtgtagag taacacataa
                                                                      180
cattgtatgc atggaaacat ggaggaacag tattacagtg tcctaccact ctaatcaaga
                                                                      240
aaaqaattac agactctgat tctacagtga tgattgaatt ctaaaaatgg taatcattag
ggcttttgat ttataanact ttgggtactt atactaaatt atggtagtta tactgccttc
                                                                      360
                                                                      420
cagtttgctt gatatatttg ttgatattaa gattcttgac ttatattttg aatgggttct
actgaaaaan gaatgatata ttettgaaga categatata catttattta caetettgat
                                                                      480
tctacaatgt agaaaatgaa ggaaatgccc caaattgtat ggtgataaaa gtcccgt
                                                                      537
```

```
<210> 75
       <211> 467
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (467)
      <223> n = A, T, C \text{ or } G
      <400> 75
caaanacaat tgttcaaaag atgcaaatga tacactactg ctgcagctca caaacacctc
                                                                         60
tgcatattac acgtacctcc tcctgctcct caagtagtgt ggtctatttt gccatcatca
                                                                        120
cctgctgtct gcttagaaga acggctttct gctgcaangg agagaaatca taacagacgg
                                                                        180
tggcacaagg aggccatctt ttcctcatcg gttattgtcc ctagaagcgt cttctgagga
                                                                        240
totagttggg ctttctttct gggtttgggc catttcantt ctcatgtgtg tactattcta
                                                                        300
tcattattgt ataacggttt tcaaaccngt gggcacncag agaacctcac tctgtaataa
                                                                        360
caatgaggaa tagccacggt gatctccagc accaaatctc tccatgttnt tccagagctc
                                                                        420
ctccagccaa cccaaatagc cgctgctatn gtgtagaaca tccctgn
                                                                        467
      <210> 76
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (400)
      <223> n = A, T, C or G
      <400> 76
aagctgacag cattcgggcc gagatgtctc gctccgtggc cttagctgtg ctcgcgctac
                                                                         60
tetetettte tggeetggag getateeage gtaeteeaaa gatteaggtt taeteaegte
                                                                        120
atccagcaga gaatggaaag tcaaatttcc tgaattgcta tgtgtctggg tttcatccat
                                                                        180
ccgacattga agttgactta ctgaagaatg gagagagaat tgaaaaagtg gagcattcag
                                                                        240
acttgtettt cagcaaggac tggtetttet atetettgta etacactgaa tteacececa
                                                                        300
ctgaaaaaga tgagtatgcc tgccgtgtga accatgtgac tttgtcacag cccaagatng
                                                                        360
ttnagtggga tcganacatg taagcagcan catgggaggt
                                                                        400
      <210> 77
      <211> 248
      <212> DNA
      <213> Homo sapien
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                         60
ccagctgccc cggcggggga tgcgaggctc ggagcaccct tgcccggctg tgattgctgc
                                                                        120
caggeactgt teateteage tittetgtee ettigeteec ggcaageget tetgetgaaa
                                                                        180
gttcatatct ggagcctgat gtcttaacga ataaaggtcc catgctccac ccgaaaaaaa
                                                                        240
aaaaaaa
                                                                        248
      <210> 78
      <211> 201
      <212> DNA
      <213> Homo sapien
      <400> 78
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                         60
tcacccagac cccgccctgc ccgtgcccca cgctgctgct aacgacagta tgatgcttac
                                                                        120
tetgetacte ggaaactatt tttatgtaat taatgtatge tttettgitt ataaatgeet
                                                                        180
gatttaaaaa aaaaaaaaaa a
                                                                        201
```

27

```
<210> 79
      <211> 552
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (552)
      <223> n = A, T, C or G
      <400> 79
tccttttgtt aggtttttga gacaacccta gacctaaact gtgtcacaga cttctgaatg
tttaggcagt gctagtaatt tcctcgtaat gattctgtta ttactttcct attctttatt
                                                                        120
cctctttctt ctgaagatta atgaagttga aaattgaggt ggataaatac aaaaaggtag
                                                                        180
tgtgatagta taagtatcta agtgcagatg aaagtgtgtt atatatatcc attcaaaatt
                                                                        240
atgeaagtta gtaattacte agggttaaet aaattaettt aatatgetgt tgaacctaet
                                                                        300
ctgttccttg gctagaaaaa attataaaca ggactttgtt agtttgggaa gccaaattga
                                                                        360
                                                                        420
taatattota tyttotaaaa yttygyotat acataaanta tnaagaaata tygaatttta
ttcccaggaa tatggggttc atttatgaat antacccggg anagaagttt tgantnaaac
                                                                        480
                                                                        540
cngttttggt taatacgtta atatgtcctn aatnaacaag gcntgactta tttccaaaaa
                                                                        552
aaaaaaaaa aa
      <210> 80
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (476)
      <223> n = A, T, C \text{ or } G
      <400> 80
acagggattt gagatgctaa ggccccagag atcgtttgat ccaaccctct tattttcaga
                                                                        120
qqqqaaaatq qqqcctaqaa qttacaqagc atctagctqg tgcgctggca cccctggcct
                                                                        180
cacacagact cccgagtagc tgggactaca ggcacacagt cactgaagca ggccctgttt
gcaattcacg ttgccacctc caacttaaac attcttcata tgtgatgtcc ttagtcacta
                                                                        240
aggttaaact ttcccaccca gaaaaggcaa cttagataaa atcttagagt actttcatac
                                                                        300
                                                                        360
tettetaagt cetetteeag ecteactitg agteeteett gggggttgat aggaaninte
tcttggcttt ctcaataaaa tctctatcca tctcatgttt aatttggtac gcntaaaaat
                                                                        420
qctqaaaaaa ttaaaatqtt ctqqtttcnc tttaaaaaaa aaaaaaaaaa aaaaaaa
                                                                        476
      <210> 81
      <211> 232
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(232)
      <223> n = A, T, C or G
      <400> 81
tttttttttttttt tatgeenten etgtggngtt attgttgetg ceaccetgga ggageecagt
ttettetqta tetttetttt etgggggate tteetggete tgeceeteea tteeeageet
                                                                        120
ctcatcccca tcttgcactt ttgctagggt tggaggcgct ttcctggtag cccctcagag
                                                                        180
actcagtcag cgggaataag tcctaggggt ggggggtgtg gcaagccggc ct
                                                                        232
      <210> 82
      <211> 383
      <212> DNA
      <213> Homo sapien
```

```
<220>
         <221> misc_feature
         <222> (1)...(383)
         <223> n = A, T, C or G
        <400> 82
  aggcgggagc agaagctaaa gccaaagccc aagaagagtg gcagtgccag cactggtgcc
                                                                                60
  agtaccagta ccaataacat gccagtgcca gtgccagcac cagtggtggc ttcagtgctg
                                                                               120
  gtgccagcct gaccgccact ctcacatttg ggctcttcgc tggccttggt ggagctggtg
                                                                               180
  ccagcaccag tggcagctct ggtgcctgtg gtttctccta caagtgagat tttagatatt
                                                                               240
  gttaatcetg ccagtettte tetteaagee agggtgeate etcagaaace tacteaacae
                                                                               300
  agcactetng geagecacta teaateaatt gaagttgaca etetgeatta aatetatttg
                                                                               360
  ccatttcaaa aaaaaaaaaa aaa
                                                                               383
        <210> 83
        <211> 494
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(494)
        <223> n = A,T,C or G
        <400> 83
. accgaattgg gaccgctggc ttataagcga tcatgtcctc cagtattacc tcaacgagca
                                                                               60
 gggagatega gtetataege tgaagaaatt tgaceegatg ggacaacaga cetgeteage
                                                                              120
 ccatcctgct cggttctccc cagatgacaa atactctcga caccgaatca ccatcaagaa
                                                                              180
 acgettcaag gtgctcatga cccagcaacc gcgccctgtc ctctgagggt ccttaaactg
                                                                              240
 atgtetttte tgecaectgt taccectegg agacteegta accaaactet teggaetgtg agecetgatg cetttttgee agecataete tttggentee agtetetegt ggegattgat
                                                                              300
                                                                              360
 tatgcttgtg tgaggcaatc atggtggcat cacccatnaa gggaacacat ttgantttt
                                                                              420
 tttcncatat tttaaattac naccagaata nttcagaata aatgaattga aaaactctta
                                                                              480
 aaaaaaaaa aaaa
                                                                              494
        <210> 84
        <211> 380
        <212> DNA
        <213> Homo sapien
        <220>
        <221> misc_feature
        <222> (1)...(380)
        <223> n = A, T, C or G
 gctggtagcc tatggcgtgg ccacggangg gctcctgagg cacgggacag tgacttccca agtatcctgc gccgcgtctt ctaccgtccc tacctgcaga tcttcgggca gattccccag
                                                                               60
                                                                              120
 gaggacatgg acgtggccct catggagcac agcaactgct cgtcggagcc cggcttctgg
                                                                              180
 gcacaccete etggggccca ggegggcace tgegtetece agtatgccaa etggetggtg
                                                                              240
 gtgctgctcc tcgtcatctt cctgctcgtg gccaacatcc tgctggtcac ttgctcattg
                                                                              300
 ccatgitcag tracacatte ggcaaagtae agggeaacag enatetetae tgggaaggee
                                                                              360
 agcgttnccg cctcatccgg
        <210> 85
        <211> 481
        <212> DNA
       <213> Homo sapien
       <220>
       <221> misc feature
```

```
<222> (1)...(481)
      <223> n = A, T, C or G
      <400> 85
gagttagete etceacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
tnccatcgtc atactgtagg tttgccacca cctcctgcat cttggggcgg ctaatatcca
                                                                       120
                                                                       180
ggaaactete aateaagtea eegtenatna aacetgtgge tggttetgte tteegetegg
tgtgaaagga tetecagaag gagtgetega tettececae acttttgatg actttattga
                                                                       240
gtcgattctg catgtccagc aggaggttgt accagctctc tgacagtgag gtcaccagcc
                                                                       300
                                                                       360
ctatcatqcc nttqaacgtg ccgaagaaca ccgagccttg tgtggggggt gnagtctcac
                                                                       420
ccagattctg cattaccaga nagccgtggc aaaaganatt gacaactcgc ccaggnngaa
aaaqaacacc teetggaaqt getngeeget eetegteent tggtggnnge gentneettt
                                                                       480
                                                                       481
      <210> 86
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(472)
      <223> n = A, T, C or G
      <400> 86
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgctg agaattcatt
                                                                       120
acttggaaaa gcaacttnaa gcctggacac tggtattaaa attcacaata tgcaacactt
taaacagtgt gtcaatctgc tcccttactt tgtcatcacc agtctgggaa taagggtatg
                                                                       180
                                                                       240
ccctattcac acctqttaaa aqqqcqctaa qcatttttqa ttcaacatct ttttttttqa
cacaagtccg aaaaaagcaa aagtaaacag ttnttaattt gttagccaat tcactttctt
                                                                       300
                                                                       360
catgggacag agccatttga tttaaaaagc aaattgcata atattgagct ttgggagctg
atatntgage ggaagantag cetttetaet teaceagaea caacteettt catattggga
                                                                       420
tgttnacnaa agttatgtct cttacagatg ggatgctttt gtggcaattc tg
                                                                       472
      <210> 87
      <211> 413
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc feature
      <222> (1) ... (413)
      <223> n = A, T, C or G
      <400> 87
                                                                        60
agaaaccagt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
tgtgtgtgcg cgcatattat atagacaggc acatctttt tacttttgta aaagcttatg
                                                                       120
                                                                       180
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                       240
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc cttgactagg
                                                                       300
                                                                       360
ggggacaaag aaaagcanaa ctgaacatna gaaacaattn cctggtgaga aattncataa
acagaaattg ggtngtatat tgaaananng catcattnaa acgtttttt ttt
      <210> 88
      <211> 448
      <212> DNA
      <213> Homo sapien
     <220>
     <221> misc_feature
     <222> (1)...(448)
     <223> n = A, T, C or G
```

```
<400> 88
 cgcagcgggt cctctctatc tagctccagc ctctcgcctg ccccactccc cgcgtcccgc
                                                                         60
 gteetageen accatggeeg ggeeeetgeg egeeeegetg eteetgetgg ceatectgge
                                                                        120
 cgtggccctg gccgtgagcc ccgcggccgg ctccagtccc ggcaagccgc cgcgcctggt
                                                                        180
 gggaggccca tggaccccgc gtggaagaag aaggtgtgcg gcgtgcactg gactttgccg
                                                                        240
 teggenanta caacaaacce geaacnactt ttacenagen egegetgeag gttgtgeege
                                                                        300
 cccaancaaa ttgttactng gggtaantaa ttcttggaag ttgaacctgg gccaaacnng
                                                                        360
tttaccagaa ccnagccaat tngaacaatt ncccctccat aacagcccct tttaaaaagg
                                                                        420
 gaancantcc tgntcttttc caaatttt
                                                                        448
      <210> 89
      <211> 463
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (463)
      <223> n = A, T, C or G
      <400> 89
gaattttgtg cactggccac tgtgatggaa ccattgggcc aggatgcttt gagtttatca
gtagtgattc tgccaaagtt ggtgttgtaa catgagtatg taaaatgtca aaaaattagc
                                                                        120
agaggtctag gtctgcatat cagcagacag tttgtccgtg tattttgtag ccttgaaqtt
                                                                        180
ctcagtgaca agttnnttct gatgcgaagt tctnattcca gtgttttagt cctttgcatc
                                                                        240
tttnatgttn agacttgcct ctntnaaatt gcttttgtnt tctgcaggta ctatctgtgg
                                                                        300
tttaacaaaa tagaannact tctctgcttn gaanatttga atatcttaca tctnaaaatn
                                                                        360
aattetete ccatannaaa acceangeee ttggganaat ttgaaaaang gnteettenn
                                                                        420
aattennana antteagntn teatacaaca naaenggane eec
                                                                        463
      <210> 90
      <211> 400
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (400)
      <223> n = A, T, C or G
      <400> 90
agggattgaa ggtctnttnt actgtcggac tgttcancca ccaactctac aagttgctgt
cttccactca ctgtctgtaa gcntnttaac ccaqactgta tcttcataaa tagaacaaat
                                                                       120
tetteaceag teacatette taggacettt ttggatteag ttagtataag etetteeact
                                                                       180
tcctttgtta agacttcatc tggtaaagtc ttaagttttg tagaaaggaa tttaattgct
                                                                       240
cgttctctaa caatgtcctc tccttgaagt atttggctga acaacccacc tnaagtccct
                                                                       300
tigtgcatcc attitaaata tacttaatag ggcattggtn cactaggtta aattctgcaa
                                                                       360
gagtcatctg tctgcaaaag ttgcgttagt atatctgcca
                                                                       400
      <210> 91
      <211> 480
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(480)
      <223> n = A, T, C or G
      <400> 91
gagctcggat ccaataatct ttgtctgagg gcagcacaca tatncagtgc catggnaact
                                                                        60
```

```
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
                                                                          120
 atgeetettt gaetaeegtg tgeeagtget ggtgattete acacacetee nneegetett
                                                                          180
 tgtggaaaaa ctggcacttg nctggaacta gcaagacatc acttacaaat tcacccacga
                                                                          240
 gacacttgaa aggtgtaaca aagcgactct tgcattgctt tttgtccctc cggcaccagt
                                                                          300
 tgtcaatact aacccgctgg tttgcctcca tcacatttgt gatctgtagc tctggataca
                                                                          360
 tctcctgaca gtactgaaga acttcttctt ttgtttcaaa agcaactctt ggtgcctgtt
                                                                          420
 ngatcaggtt cocatttocc agtccgaatg ttcacatggc atatnttact tcccacaaaa
                                                                          480
       <210> 92
       <211> 477
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (477)
       <223> n = A, T, C or G
      <400> 92
atacagecea nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteaet
                                                                           60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcctt
                                                                          120
cccacgcagg cagcagcggg gccggtcaat gaactccact cgtggcttgg ggttgacggt
                                                                          180
taantgcagg aagaggctga ccacctcgcg gtccaccagg atgcccgact gtgcgggacc
                                                                          240
tgcagcgaaa ctcctcgatg gtcatgagcg ggaagcgaat gangcccagg gccttgccca gaaccttccg cctgttctct ggcgtcacct gcagctgctg ccgctnacac tcggcctcgg
                                                                          300
                                                                          360
accageggae aaacggegtt gaacageege accteaegga tgeeeantgt gtegegetee
                                                                          420
aggaacggen ccagegtgte caggteaatg teggtgaane eteegegggt aatggeg
                                                                          477
      <210> 93
      <211> 377
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(377)
      <223> n = A, T, C or G
      <400> 93
gaacggctgg accttgcctc gcattgtgct gctggcagga ataccttggc aagcagctcc
agtocgagea gooccagaco gotgoogooc gaagotaago otgoototgg cottoccoto
                                                                          120
cgcctcaatg cagaaccant agtgggagca ctgtgtttag agttaagagt gaacactgtn
                                                                          180
tgattttact tgggaatttc ctctgttata tagcttttcc caatgctaat ttccaaacaa
                                                                          240
caacaacaaa ataacatgtt tgcctgttna gttgtataaa agtangtgat tctgtatnta
                                                                          300
aagaaaatat tactgttaca tatactgctt gcaanttctg tatttattgg tnctctggaa
                                                                          360
ataaatatat tattaaa
                                                                          377
    · <210> 94
      <211> 495
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(495)
      <223> n = A, T, C or G
ccctttgagg ggttagggtc cagttcccag tggaagaaac aggccaggag aantgcgtgc
                                                                          60
cgagctgang cagatttccc acagtgaccc cagagccctg ggctatagtc tctgaccct
                                                                         120
ccaaggaaag accaccttct ggggacatgg gctggagggc aggacctaga ggcaccaagg
                                                                         180
gaaggcccca ttccggggct gttccccgag gaggaaggga aggggctctg tgtgccccc
                                                                         240
```

acgaggaana qqccctqant cctqqqatca nacacccctt cacqtqtatc cccacacaaa

```
tgcaagctca ccaaggtccc ctctcagtcc cttccctaca ccctgaacgg ncactggccc
                                                                          360
acacccaccc agancancca cccgccatgg ggaatgtnct caaggaatcg cngggcaacg tggactctng tcccnnaagg gggcagaatc tccaatagan gganngaacc cttgctnana
                                                                          420
                                                                          480
aaaaaaana aaaaa
                                                                          495
      <210> 95
      <211> 472
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (472)
      <223> n = A, T, C or G
      <400> 95
ggttacttqq tttcattqcc accacttagt ggatqtcatt tagaaccatt ttgtctgctc
                                                                          120
cctctggaag ccttgcgcag agcggacttt gtaattgttg gagaataact gctgaatttt
tagetgtttt gagttgatte geaceactge accaeaacte aatatgaaaa etatttnact
                                                                          180
tatttattat cttgtgaaaa gtatacaatg aaaattttgt tcatactgta tttatcaagt
                                                                          240
                                                                          300
atgatgaaaa gcaatagata tatattottt tattatgttn aattatgatt gccattatta
atcggcaaaa tgtggagtgt atgttctttt cacagtaata tatgcctttt gtaacttcac
                                                                          360
ttggttattt tattgtaaat gaattacaaa attcttaatt taagaaaatg gtangttata
                                                                          420
tttanttcan taatttcttt ccttgtttac gttaattttg aaaagaatgc at
                                                                          472
      <210> 96
      <211> 476
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (476)
      <223> n = A, T, C or G
      <400> 96
ctgaagcatt tettcaaact tntetaettt tgteattgat acetgtagta agttgacaat
                                                                           60
gtggtgaaat ttcaaaatta tatgtaactt ctactagttt tactttctcc cccaagtctt
                                                                          120
ttttaactca tgatttttac acacacaatc cagaacttat tatatagcct ctaagtcttt
attetteaca gtagatgatg aaagagteet ecagtgtett gngcanaatg ttetagntat
                                                                          240
agctggatac atacngtggg agttctataa actcatacct cagtgggact naaccaaaat
                                                                          300
tgtgttagtc tcaattccta ccacactgag ggagcctccc aaatcactat attcttatct
                                                                          360
gcaggtactc ctccagaaaa acngacaggg caggcttgca tgaaaaagtn acatctgcgt
                                                                          420
tacaaagtet atetteetea nangtetgtn aaggaacaat ttaatettet agettt
      <210> 97
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (479)
      <223> n = A, T, C or G
      <400> 97
                                                                           60
actettteta atgetgatat gatettgagt ataagaatge atatgteact agaatggata
                                                                          120
aaataatgct gcaaacttaa tgttcttatg caaaatggaa cgctaatgaa acacagctta
caatcgcaaa tcaaaactca caagtgctca tctgttgtag atttagtgta ataagactta
                                                                          180
gattgtgctc cttcggatat gattgtttct canatcttgg gcaatnttcc ttagtcaaat
                                                                          240
caggetacta quattetett attegatatn teagageate aaatttttaa naatacaett
                                                                          300
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36

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Cys Cys Pro Cys Arg Ala Arg Leu Ala Phe Arg Asn Leu Gly Ala Leu 245 250 255 Leu Pro Arg Leu His Gln Leu Cys Cys Arg Met Pro Arg Thr Leu Arg 260 265 270 Arg Leu Phe Val Ala Glu Leu Cys Ser Trp Met Ala Leu Met Thr Phe 280 285 Thr Leu Phe Tyr Thr Asp Phe Val Gly Glu Gly Leu Tyr Gln Gly Val 295 Pro Arg Ala Glu Pro Gly Thr Glu Ala Arg Arg His Tyr Asp Glu Gly 310 315 Val Arg Met Gly Ser Leu Gly Leu Phe Leu Gln Cys Ala Ile Ser Leu 330 325 335 Val Phe Ser Leu Val Met Asp Arg Leu Val Gln Arg Phe Gly Thr Arg 340 345 Ala Val Tyr Leu Ala Ser Val Ala Ala Phe Pro Val Ala Ala Gly Ala 355 360 365 Thr Cys Leu Ser His Ser Val Ala Val Val Thr Ala Ser Ala Ala Leu 375 380 Thr Gly Phe Thr Phe Ser Ala Leu Gln Ile Leu Pro Tyr Thr Leu Ala 390 395 Ser Leu Tyr His Arg Glu Lys Gln Val Phe Leu Pro Lys Tyr Arg Gly 405 410 415 Asp Thr Gly Gly Ala Ser Ser Glu Asp Ser Leu Met Thr Ser Phe Leu 420 425 430 Pro Gly Pro Lys Pro Gly Ala Pro Phe Pro Asn Gly His Val Gly Ala 435 440 445 Gly Gly Ser Gly Leu Leu Pro Pro Pro Pro Ala Leu Cys Gly Ala Ser 450 455 460 Ala Cys Asp Val Ser Val Arg Val Val Val Gly Glu Pro Thr Glu Ala 470 475 - 480 Arg Val Val Pro Gly Arg Gly Ile Cys Leu Asp Leu Ala Ile Leu Asp 485 490 495 Ser Ala Phe Leu Leu Ser Gln Val Ala Pro Ser Leu Phe Met Gly Ser 510 500 505 Ile Val Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala 515 520 525 Gly Leu Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp 535 Lys Ser Asp Leu Ala Lys Tyr Ser Ala

<210> 114

<211> 241

<212> PRT

<213> Homo sapien

<400> 114

Met Gln Cys Phe Ser Phe Ile Lys Thr Met Met Ile Leu Phe Asn Leu Leu Ile Phe Leu Cys Gly Ala Ala Leu Leu Ala Val Gly Ile Trp Val 25 Ser Ile Asp Gly Ala Ser Phe Leu Lys Ile Phe Gly Pro Leu Ser Ser 35 45 40 Ser Ala Met Gln Phe Val Asn Val Gly Tyr Phe Leu Ile Ala Ala Gly 55 Val Val Val Phe Ala Leu Gly Phe Leu Gly Cys Tyr Gly Ala Lys Thr 65 70 75 80 Glu Ser Lys Cys Ala Leu Val Thr Phe Phe Phe Ile Leu Leu Ile 85 90 Phe Ile Ala Glu Val Ala Ala Ala Val Val Ala Leu Val Tyr Thr Thr 100 105 110 Met Ala Glu His Phe Leu Thr Leu Leu Val Val Pro Ala Ile Lys Lys

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120
Asp Tyr Gly Ser Gln Glu Asp Phe Thr Gln Val Trp Asn Thr Thr Met
    130
                        135
                                             140
Lys Gly Leu Lys Cys Cys Gly Phe Thr Asn Tyr Thr Asp Phe Glu Asp
145
                   150
                                         155
Ser Pro Tyr Phe Lys Glu Asn Ser Ala Phe Pro Pro Phe Cys Cys Asn
                165
                                     170
Asp Asn Val Thr Asn Thr Ala Asn Glu Thr Cys Thr Lys Gln Lys Ala
            180
                                 185
His Asp Gln Lys Val Glu Gly Cys Phe Asn Gln Leu Leu Tyr Asp Ile
                             200
        195
                                                 205
Arg Thr Asn Ala Val Thr Val Gly Gly Val Ala Ala Gly Ile Gly Gly
                        215
                                             220
Leu Glu Leu Ala Ala Met Ile Val Ser Met Tyr Leu Tyr Cys Asn Leu
225
Gln
      <210> 115
      <211> 366
      <212> DNA
      <213> Homo sapien
      <400> 115
getetttete teeceteete tgaatttaat tettteaaet tgeaatttge aaggattaea
                                                                         60
                                                                        120
catttcactg tgatgtatat tgtgttgcaa aaaaaaaaa gtgtctttgt ttaaaattac
ttggtttgtg aatccatctt gctttttccc cattggaact agtcattaac ccatctctga
                                                                        180
actggtagaa aaacatctga agagctagtc tatcagcatc tgacaggtga attggatggt
                                                                        240
totcagaaco atttcaccca gacagootgt ttotatootg tttaataaat tagtttgggt
                                                                        300
tototacatg cataacaaac cotgotocaa totgtoacat aaaagtotgt gaottgaagt
                                                                        360
ttagtc
                                                                        366
      <210> 116
      <211> 282
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (282)
      <223> n = A, T, C or G
      <400> 116
acaaagatga accatttcct atattatagc aaaattaaaa tctacccgta ttctaatatt
                                                                         60
gagaaatgag atnaaacaca atnttataaa gtctacttag agaagatcaa gtgacctcaa
                                                                        120
agactttact attttcatat tttaagacac atgatttatc ctattttagt aacctggttc
atacgttaaa caaaggataa tgtgaacagc agagaggatt tgttggcaga aaatctatgt
                                                                        240
                                                                        282
tcaatctnga actatctana tcacagacat ttctattcct tt
      <210> 117
      <211> 305
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (305)
      <223> n = A, T, C or G
      <400> 117
acacatgtcg cttcactgcc ttcttagatg cttctggtca acatanagga acagggacca
                                                                        60
                                                                        120
tatttatcct ccctcctgaa acaattgcaa aataanacaa aatatatgaa acaattgcaa
```

```
aataaggcaa aatatatgaa acaacaggtc tcgagatatt ggaaatcagt caatgaagga
                                                                        180
tactgatece tgateactgt cetaatgeag gatgtgggaa acagatgagg teacetetgt
                                                                        240
gactgcccca gcttactgcc tgtagagagt ttctangctg cagttcagac agggagaaat
                                                                        300
tgggt
                                                                        305
      <210> 118
      <211> 71
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(71)
      <223> n = A,T,C or G
      <400> 118
accaaggtgt ntgaatctct gacgtgggga tctctgattc ccgcacaatc tgagtggaaa
                                                                         60
aantcctggg t
                                                                         71
      <210> 119
      <211> 212
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (212)
      <223> n = A, T, C or G
      <400> 119
actccggttg gtgtcagcag cacgtggcat tgaacatngc aatgtggagc ccaaaccaca
                                                                         60
gaaaatgggg tgaaattggc caactttcta tnaacttatg ttggcaantt tgccaccaac
                                                                        120
agtaagetgg ccettetaat aaaagaaaat tgaaaggttt ctcactaane ggaattaant
                                                                        180
                                                                        212
aatggantca aganactccc aggcctcagc qt
      <210> 120
      <211> 90
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (90)
      <223> n = A,T,C or G
      <400> 120
actcgttgca natcaggggc cccccagagt caccgttgca ggagtccttc tggtcttgcc
                                                                         60
ctccgccggc gcagaacatg ctggggtggt
                                                                         90
      <210> 121
      <211> 218
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (218)
      <223> n = A,T,C or G
      <400> 121
tgtancgtga anacgacaga nagggttgtc aaaaatggag aanccttgaa gtcattttga
                                                                         60
gaataagatt tgctaaaaga tttggggcta aaacatggtt attgggagac atttctgaag
                                                                        120
```

	aaattangga tcatgtgggg			ggaattcctt	tacgatngcc	180 218
<211 <212	> 122 > 171 > DNA > Homo sapi	en				
taggggtgta catttgttag	> 122 tgcaactgta ctcatggaac gcggggtcat	aggaagtcgg	atggtggggc	atcttcagtg	ctgcatgagt	60 120 171
<211 <212	> 123 > 76 > DNA > Homo sapi	en				
<222	> misc_feat > (1)(76 > n = A,T,C	)				٠٠
	> 123 agacnacaga ttgtgt	atggtgtgtg	ctgtgctatc	caggaacaca	tttattatca	60 76
<211 <212	> 124 > 131 > DNA > Homo sapi	en			•••	
acctttcccc	> 124 aaggccaatg ggtcatatgg t					60 120 131
<211 <212	> 125 > 432 > DNA > Homo sapi	en				
actttatcta cttgaaaaag ctacagtctg ttgcctcacc ctcttgaagt catggtgggg	> 125 ctggctatga aggtgatagc catttggcag aaacaaaagt atcagtcact gtcttgcatc cagaaccact gt	tcttcagagg aaatgaagat gaaacaactg tttgagaatg tgtaagaatg	acttgtgact gaatttggat agagaaaatt tttcttagtt gaattgattt	tttgctcaga taaatgagga ttcaggaaaa actgcatact tgcttttgca	tgctgaagaa tgctgaagat aagacagtgg tcatggatcc agaatctcag	60 120 180 240 300 360 420 432
<211 <212	> 126 > 112 > DNA > Homo sapie	en		·		
acacaacttg	> 126 aatagtaaaa atatttcccc	tagaaactga ccagggatca	gctgaaattt ccaaatattt	ctaattcact ataaaaattt	ttctaaccat gt	60 112

<210> 127

44

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<211> 54
       <212> DNA
       <213> Homo sapien
       <400> 127
 accacgaaac cacaaacaag atggaagcat caatccactt gccaagcaca gcag
                                                                             54
       <210> 128
       <211> 323
       <212> DNA
       <213> Homo sapien
       <400> 128
acctcattag taattgtttt gttgtttcat ttttttctaa tgtctcccct ctaccagctc
acctgagata acagaatgaa aatggaagga cagccagatt tctcctttgc tctctgctca
                                                                            120
ttctctctga agtctaggtt acccattttg gggacccatt ataggcaata aacacagttc
                                                                            180
ccaaagcatt tggacagttt cttgttgtgt tttagaatgg ttttcctttt tcttagcctt
                                                                            240
ttcctgcaaa aggctcactc agtcccttgc ttgctcagtg gactgggctc cccagggcct
                                                                            300
aggetgeett etttteeatg tee
                                                                            323
       <210> 129
       <211> 192
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (192)
       <223> n = A, T, C or G
      <400> 129
acatacatgt gtgtatattt ttaaatatca cttttgtatc actctgactt tttagcatac
                                                                             60
tgaaaacaca ctaacataat ttntgtgaac catgatcaga tacaacccaa atcattcatc
                                                                            120
tagcacattc atctgtgata naaagatagg tgagtttcat ttccttcacg ttggccaatg
                                                                            180
gataaacaaa gt
                                                                            192
      <210> 130
      <211> 362
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (362)
      <223> n = A, T, C \text{ or } G
ccctttttta tggaatgagt agactgtatg tttgaanatt tanccacaac ctctttgaca
                                                                            60
tataatgacg caacaaaaag gtgctgttta gtcctatggt tcagtttatg cccctgacaa
                                                                           120
gtttccattg tgttttgccg atcttctggc taatcgtggt atcctccatg ttattagtaa
                                                                           180
ttctgtattc cattttgtta acgcctggta gatgtaacct gctangaggc taactttata cttatttaaa agctcttatt ttgtggtcat taaaatggca atttatgtgc agcactttat
                                                                           240
                                                                           300
tgcagcagga agcacgtgtg ggttggttgt aaagctcttt gctaatctta aaaagtaatg
                                                                           360
gg
                                                                           362
      <210> 131
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
```

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<222> (1)...(332)
      <223> n = A,T,C or G
      <400> 131
ctttttgaaa gatcgtgtcc actcctgtgg acatcttgtt ttaatggagt ttcccatgca.
                                                                         60
gtangactgg tatggttgca gctgtccaga taaaaacatt tgaagagctc caaaatgaga
                                                                        180
gttctcccag gttcgccctg ctgctccaag tctcagcagc agcctctttt aggaggcatc
ttctgaacta gattaaggca gcttgtaaat ctgatgtgat ttggtttatt atccaactaa
                                                                        240
cttccatctg ttatcactgg agaaagccca gactccccan gacnggtacg gattgtgggc
                                                                        300
atanaaggat tgggtgaagc tggcgttgtg gt
                                                                        332
      <210> 132
      <211> 322
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (322)
      <223> n = A, T, C or G
      <400> 132
acttttgcca ttttgtatat ataaacaatc ttgggacatt ctcctgaaaa ctaggtgtcc
                                                                         60
                                                                        120
agtggctaag agaactcgat ttcaagcaat tctgaaagga aaaccagcat gacacagaat
ctcaaattcc caaacagggg ctctgtggga aaaatgaggg aggacctttg tatctcgggt
                                                                        180
tttagcaagt taaaatgaan atgacaggaa aggcttattt atcaacaaag agaagagttg
                                                                        240
                                                                        300
ggatgcttct aaaaaaaact ttggtagaga aaataggaat gctnaatcct agggaagcct
gtaacaatct acaattggtc ca
                                                                        322
      <210> 133
      <211> 278
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (278)
      <223> n = A, T, C or G
      <400> 133
                                                                         60
acaagcette acaagtttaa etaaattggg attaatettt etgtanttat etgeataatt
                                                                        120
cttgtttttc tttccatctg gctcctgggt tgacaatttg tggaaacaac tctattgcta
ctatttaaaa aaaatcacaa atctttccct ttaagctatg ttnaattcaa actattcctg
                                                                        180
ctattcctgt tttgtcaaag aaattatatt tttcaaaata tgtntatttg tttgatgggt
                                                                        240
                                                                        278
cccacgaaac actaataaaa accacagaga ccagcctg
      <210> 134
      <211> 121
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(121)
      <223> n = A, T, C or G
      <400> 134
                                                                         60
gtttanaaaa cttgtttagc tccatagagg aaagaatgtt aaactttgta ttttaaaaca
                                                                        120
tgattctctg aggttaaact tggttttcaa atgttatttt tacttgtatt ttgcttttgg
                                                                        121
```

<210> 135

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<211> 350
       <212> DNA
       <213> Homo sapien
       <220>
      <221> misc feature
       <222> (1) ... (350)
      <223> n = A,T,C or G
      <400> 135
acttanaacc atgcctagca catcagaatc cctcaaagaa catcagtata atcctatacc
atancaagtg gtgactggtt aagcgtgcga caaaggtcag ctggcacatt acttgtgtgc
                                                                          120
aaacttgata cttttgttct aagtaggaac tagtatacag tncctaggan tggtactcca
                                                                          180
gggtgcccc caactcctgc agccgctcct ctgtgccagn ccctgnaagg aactttcgct
                                                                          240
ccacctcaat caagecetgg gecatgetac etgeaattgg etgaacaaac gtttgetgag
                                                                          300
ttcccaagga tgcaaagcct ggtgctcaac tcctggggcg tcaactcagt
                                                                          350
      <210> 136
      <211> 399
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      \langle 222 \rangle (1)...(399)
\langle 223 \rangle n = A,T,C or G
      <400> 136
tgtaccgtga agacgacaga agttgcatgg cagggacagg gcagggccga ggccagggtt
gctgtgattg tatccgaata ntcctcgtga gaaaagataa tgagatgacg tgagcagcct
                                                                          120
gcagacttgt gtctgccttc aanaagccag acaggaaggc cctgcctgcc ttggctctga
                                                                          180
cctggcggcc agccagccag ccacaggtgg gcttcttcct tttgtggtga caacnccaag
                                                                          240
aaaactgcag aggcccaggg tcaggtgtna gtgggtangt gaccataaaa caccaggtgc
                                                                          300
teccaggaac eegggcaaag gecateeeca eetacageca geatgeeeac tggegtgatg
                                                                          360
ggtgcagang gatgaagcag ccagntgttc tgctgtggt
                                                                          399
      <210> 137
      <211> 165
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (165)
      <223> n = A, T, C or G
actggtgtgg tngggggtga tgctggtggt anaagttgan gtgacttcan gatggtgtgt
                                                                          60
ggaggaagtg tgtgaacgta gggatgtaga ngttttggcc gtgctaaatg agcttcqqqa
                                                                          120
ttggctggtc ccactggtgg tcactgtcat tggtggggtt cctgt
                                                                          165
      <210> 138
      <211> 338
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(338)
      <223> n = A, T, C or G
      <400> 138
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```
actcactgga atgccacatt cacaacagaa tcagaggtct gtgaaaacat taatggctcc
                                                                           60
ttaacttctc cagtaagaat cagggacttg aaatggaaac gttaacagcc acatgcccaa
                                                                          120
tgctgggcag tctcccatgc cttccacagt gaaagggctt gagaaaaatc acatccaatg tcatgtgttt ccagccacac caaaaggtgc ttggggtgga gggctggggg catananggt
                                                                          180
                                                                          240
cangecteag gaageeteaa gtteeattea getttgeeae tgtacattee ceatntttaa
                                                                          300
aaaaactgat gcctttttt ttttttttt taaaattc
                                                                          338
       <210> 139
      <211> 382
       <212> DNA
      <213> Homo sapien
      <400> 139
gggaatettg gtttttggca tetggtttge etatageega ggecaetttg acagaacaaa
                                                                           60
gaaagggact togagtaaga aggtgattta cagccagcot agtgcccgaa gtgaaggaga
                                                                          120
atteaaacag acctegteat teetggtgtg ageetggteg geteacegee tateatetge
                                                                          180
atttgcctta ctcaggtgct accggactct ggcccctgat gtctgtagtt tcacaggatg
                                                                          240
ccttatttgt cttctacacc ccacagggcc ccctacttct tcggatgtgt ttttaataat
                                                                          300
gtcagctatg tgccccatcc tccttcatgc cctccctccc tttcctacca ctgctgagtg
                                                                          360
gcctggaact tgtttaaagt gt
                                                                          382
      <210> 140
      <211> 200
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(200)
      <223> n = A, T, C or G
      <400> 140
accaaanctt ctttctgttg tgttngattt tactataggg gtttngcttn ttctaaanat
                                                                           60
actittcatt taacanctit tgttaagtgt caggetgcac tttgctccat anaattattg
                                                                          120
ttttcacatt tcaacttgta tgtgtttgtc tcttanagca ttggtgaaat cacatatttt
                                                                          180
atattcagca taaaggagaa
                                                                          200
      <210> 141
      <211> 335
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (335)
      <223> n = A, T, C or G
      <400> 141
actttatttt caaaacactc atatgttgca aaaaacacat agaaaaataa agtttggtgg
                                                                           60
gggtgctgac taaacttcaa gtcacagact tttatgtgac agattggagc agggtttgtt
                                                                          120
atgcatgtag agaacccaaa ctaatttatt aaacaggata gaaacaggct gtctgggtga
                                                                          180
aatggttctg agaaccatcc aattcacctg tcagatgctg atanactagc tcttcagatg
                                                                          240
tttttctacc agttcagaga tnggttaatg actanttcca atggggaaaa agcaagatgg
                                                                          300
attcacaaac caagtaattt taaacaaaga cactt
                                                                          335
      <210> 142
      <211> 459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
```

```
<222> (1)...(459)
      <223> n = A, T, C or G
      <400> 142
accaggitaa tattgccaca tatatccttt ccaattgcgg gctaaacaga cgtgtattta
                                                                          60
gggttgttta aagacaaccc agcttaatat caagagaaat tgtgaccttt catggagtat
                                                                        120
ctgatggaga aaacactgag ttttgacaaa tcttatttta ttcagatagc agtctgatca
                                                                        180
cacatggtcc aacaacactc aaataataaa tcaaatatna tcagatgtta aagattggtc
                                                                         240
ttcaaacatc atagccaatg atgccccgct tgcctataat ctctccqaca taaaaccaca
                                                                         300
tcaacacctc agtggccacc aaaccattca gcacagcttc cttaactgtg agctgtttga
                                                                        360
agetaccagt etgageacta ttgactatnt ttttcanget etgaataget etagggatet
                                                                        420
cagcangggt gggaggaacc agctcaacct tggcgtant
                                                                        459
      <210> 143
      <211> 140
      <212> DNA
      <213> Homo sapien
      <400> 143
acattteett ceaceaaqte aggaeteetq qettetqtqq qaqttettat cacetqaqqq
                                                                         60
aaatccaaac agtctctcct agaaaggaat agtgtcacca accccaccca tctccctgag
                                                                        120
accatecgae tteeetgtgt
                                                                        140
      <210> 144
      <211> 164
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(164)
      <223> n = A, T, C or G
      <400> 144
acttcagtaa caacatacaa taacaacatt aagtgtatat tgccatcttt gtcattttct
                                                                         60
atctatacca ctctcccttc tgaaaacaan aatcactanc caatcactta tacaaatttg
                                                                        120
aggcaattaa tocatatttg ttttcaataa ggaaaaaaag atgt
                                                                        164
      <210> 145
      <211> 303
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(303)
      <223> n = A, T, C \text{ or } G
acgtagacca tccaactttg tatttgtaat ggcaaacatc cagnagcaat tcctaaacaa
                                                                         60
actggagggt atttataccc aattatccca ttcattaaca tgccctcctc ctcaggctat
                                                                        120
gcaggacage tatcataagt cggcccagge atccagatac taccatttqt ataaacttca
                                                                        180
gtaggggagt ccatccaagt gacaggtcta atcaaaggag gaaatggaac ataagcccag
                                                                        240
tagtaaaatn ttgcttagct gaaacagcca caaaagactt accgccgtgg tgattaccat
                                                                        300
                                                                        303
      <210> 146
      <211> 327
      <212> DNA
      <213> Homo sapien
      <220>
```

```
<221> misc_feature
      <222> (1) ... (327)
      <223> n = A, T, C or G
      <400> 146
actgcagete aattagaagt ggtetetgae ttteateane tteteeetgg geteeatgae
                                                                         60
actggcctgg agtgactcat tgctctggtt ggttgagaga gctcctttgc caacaggcct
                                                                        120
ccaagtcagg gctgggattt gtttcctttc cacattctag caacaatatg ctggccactt
                                                                        180
cctgaacagg gagggtggga ggagccagca tggaacaagc tgccactttc taaagtagcc
                                                                        240
agacttgccc ctgggcctgt cacacctact gatgaccttc tgtgcctgca ggatggaatg
                                                                         300
taggggtgag ctgtgtgact ctatggt
                                                                         327
      <210> 147
      <211> 173
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(173)
      <223> n = A, T, C or G
      <400> 147
acattgtttt tttgagataa agcattgana gagctctcct taacgtgaca caatggaagg
                                                                         60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                        120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gtt
                                                                        173
      <210> 148
      <211> 477
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (477)
      <223> n = A, T, C or G
      <400> 148
acaaccactt tatctcatcg aatttttaac ccaaactcac tcactgtgcc tttctatcct
atgggatata ttatttgatg ctccatttca tcacacatat atgaataata cactcatact
                                                                        120
gccctactac ctgctqcaat aatcacattc ccttcctgtc ctgaccctga agccattggg
                                                                        180
gtggtcctag tggccatcag tccangcctg caccttgage cettgagete cattgctcae
                                                                        240
nccancccac ctcaccgacc ccatcctctt acacagctac ctccttgctc tctaacccca
                                                                        300
tagattatnt ccaaattcag tcaattaagt tactattaac actctacccg acatgtccag
caccactggt aagcettete cagecaacae acacacaeae acacneacae acacacatat
                                                                        420
\verb|ccaggcacag| gctacctcat| \verb|cttcacaatc| acccctttaa| ttaccatgct| \verb|atggtgg|
                                                                        477
      <210> 149
      <211> 207
      <212> DNA
      <213> Homo sapien
      <400> 149
acagttgtat tataatatca agaaataaac ttgcaatgag agcatttaag agggaagaac
                                                                         60
taacqtattt tagagagcca aggaaggttt ctgtggggag tgggatgtaa ggtggggcct
                                                                        120
                                                                        180
gatgataaat aagagtcagc caggtaagtg ggtggtgtgg tatgggcaca gtgaagaaca
                                                                        207
tttcaggcag agggaacagc agtgaaa
      <210> 150
     <211> 111
      <212> DNA
      <213> Homo sapien
```

```
<220>
       <221> misc_feature
       <222> (1)...(111)
       <223> n = A, T, C or G
       <400> 150
accttgattt cattgctgct ctgatggaaa cccaactatc taatttagct aaaacatggg
                                                                           60
cacttaaatg tggtcagtgt ttggacttgt taactantgg catctttggg t
                                                                          111
       <210> 151
       <211> 196
       <212> DNA
       <213> Homo sapien
      <400> 151
agcgcggcag gtcatattga acattccaga tacctatcat tactcgatgc tgttgataac
                                                                           60
agcaagatgg ctttgaactc agggtcacca ccagctattg gaccttacta tgaaaaccat
                                                                           120
ggataccaac cggaaaaccc ctatcccgca cagcccactg tggtccccac tgtctacqag
                                                                          180
gtgcatccgg ctcagt
                                                                          196
      <210> 152
      <211> 132
      <212> DNA
      <213> Homo sapien
      <400> 152
acagcacttt cacatgtaag aagggagaaa ttcctaaatg taggagaaag ataacagaac
                                                                           60
cttccccttt tcatctagtg gtggaaacct gatgctttat gttgacagga ataqaaccag
                                                                          120
gagggagttt gt
                                                                          132
      <210> 153
      <211> 285
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(285)
      <223> n = A, T, C or G
      <400> 153
acaanaccca nganaggcca ctggccgtgg tgtcatggcc tccaaacatg aaagtgtcag
cttctgctct tatgtcctca tctgacaact ctttaccatt tttatcctcg ctcagcagga
                                                                          120
gcacatcaat aaagtccaaa gtcttggact tggccttggc ttggaggaag tcatcaacac
                                                                          180
cctggctagt gagggtgcgg cgccgctcct ggatgacggc atctgtgaag tcgtgcacca
                                                                          240
gtctgcaggc cctgtggaag cgccgtccac acggagtnag gaatt
                                                                          285
      <210> 154
      <211> 333
      <212> DNA
      <213> Homo sapien
      <400> 154
accacagtcc tgttgggcca gggcttcatg accctttctg tgaaaagcca tattatcacc accccaaatt tttccttaaa tatctttaac tgaaggggtc agcctcttga ctgcaaagac
                                                                           6Ò.
                                                                          120
cctaagccgg ttacacagct aactcccact ggccctgatt tgtgaaattg ctgctgcctg
                                                                          180
attggcacag gagtcgaagg tgttcagctc ccctcctccg tggaacgaga ctctgatttg
                                                                          240
agtttcacaa attctcgggc cacctcgtca ttgctcctct gaaataaaat ccggaqaatg
                                                                          300
gtcaggcctg tctcatccat atggatcttc cgg
                                                                          333
```

```
<211> 308
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(308)
      <223> n = A, T, C or G
      <400> 155
actggaaata ataaaaccca catcacagtg ttgtgtcaaa gatcatcagg gcatggatgg
                                                                         60
gaaagtgctt tgggaactgt aaagtgccta acacatgatc gatgattttt gttataatat
                                                                        120
ttgaatcacg gtgcatacaa actotectgc ctgctcctcc tgggccccag ccccagcccc
                                                                        180
                                                                        240
atcacagete actgetetgt teatecagge ecageatgta gtggetgatt ettettgget
                                                                        300
gcttttagcc tccanaagtt tctctgaagc caaccaaacc tctangtgta aggcatgctg
                                                                        308
gccctggt
      <210> 156
      <211> 295
      <212> DNA
      <213> Homo sapien
      <400> 156
accttgctcg gtgcttggaa catattagga actcaaaata tgagatgata acagtgccta
                                                                         60
ttattgatta ctgagagaac tgttagacat ttagttgaag attttctaca caggaactga
                                                                        120
gaataggaga ttatgtttgg ccctcatatt ctctcctatc ctccttgcct cattctatgt
                                                                        180
ctaatatatt ctcaatcaaa taaggttagc ataatcagga aatcgaccaa ataccaatat
                                                                        240
                                                                        295
aaaaccagat gtctatcctt aagattttca aatagaaaac aaattaacag actat
      <210> 157
      <211> 126
      <212> DNA
      <213> Homo sapien
      <400> 157
                                                                         60
acaagtttaa atagtgctgt cactgtgcat gtgctgaaat gtgaaatcca ccacatttct
gaagagcaaa acaaattctg tcatgtaatc tctatcttgg gtcgtgggta tatctgtccc
                                                                        120
                                                                        126
      <210> 158
      <211> 442
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(442)
      <223> n = A, T, C or G
      <400> 158
acceactggt cttggaaaca cccatcctta atacgatgat ttttctgtcg tgtgaaaatg
                                                                         60
                                                                        120
aanccagcag gctgccccta gtcagtcctt ccttccagag aaaaagagat ttgagaaagt
                                                                        180
gcctgggtaa ttcaccatta atttcctccc ccaaactctc tgagtcttcc cttaatattt
                                                                        240
ctggtggttc tgaccaaagc aggtcatggt ttgttgagca tttggggatcc cagtgaagta
natgtttgta gccttgcata cttagccctt cccacgcaca aacggagtgg cagagtggtg
                                                                        300
ccaaccctgt tttcccagtc cacgtagaca gattcacagt gcggaattct ggaagctgga
                                                                        360
                                                                        420
nacagacggg ctctttgcag agccgggact ctgagangga catgagggcc tctgcctctg
                                                                        442
tgttcattct ctgatgtcct gt
      <210> 159
      <211> 498
      <212> DNA
```

```
<213> Homo sapien
       <221> misc feature
       <222> (1) ... (498)
       <223> n = A, T, C or G
      <400> 159
acttccaggt aacgttgttg tttccgttga gcctgaactg atgggtgacg ttgtaggttc
                                                                         60
tocaacaaga actgaggttg cagagcgggt agggaagagt gctqttccag ttqcacctqq
                                                                        120
gctgctgtgg actgttgttg attcctcact acggcccaag gttgtggaac tggcanaaag
                                                                        180
gtgtgttgtt gganttgagc tcgggcggct gtggtaggtt gtgggctctt caacaggggc
                                                                        240
tgctgtggtg ccgggangtg aangtgttgt gtcacttgag cttggccagc tctggaaagt
                                                                        300
antanattet teetgaagge eagegettgt ggagetggea ngggteantg ttgtgtgtaa
                                                                        360
cgaaccagtg ctgctgtggg tgggtgtana tcctccacaa agcctgaagt tatggtgtcn
                                                                        420
tcaggtaana atgtggtttc agtgtccctg ggcngctgtg gaaggttgta nattgtcacc
                                                                        480
aagggaataa gctgtggt
                                                                        498
      <210> 160
      <211> 380
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (380)
      <223> n = A, T, C or G
      <400> 160
acctgcatcc agcttccctg ccaaactcac aaggagacat caacctctag acagggaaac
                                                                         60
agetteagga taetteeagg agacagagee accageagea aaacaaatat teecatgeet
                                                                        120
ggagcatggc atagaggaag ctganaaatg tggggtctga ggaagccatt tgagtctggc
                                                                        180
cactagacat ctcatcagec acttgtgtga agagatgece catgacecca gatgeetete
                                                                        240
ccaccettae etecatetea cacacttgag etttecacte tgtataatte taacateetg
                                                                        300
gagaaaaatg gcagtttgac cgaacctgtt cacaacggta gaggctgatt tctaacgaaa
                                                                        360
cttgtagaat gaagcctgga
                                                                        380
      <210> 161
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 161
actocacate ecetetgage aggeggttgt egtteaaggt gtatttggee ttgeetgtea
                                                                        60
cactgtccac tggcccctta tccacttggt gcttaatccc tcgaaagagc atgt
                                                                       114
      <210> 162
      <211> 177
      <212> DNA
      <213> Homo sapien
      <400> 162
actttctqaa tcqaatcaaa tqatacttaq tqtaqtttta atatcctcat atatatcaaa
                                                                        60
gttttactac tctgataatt ttgtaaacca ggtaaccaga acatccagtc atacagcttt
                                                                       120
tggtgatata taacttggca ataacccagt ctggtgatac ataaaactac tcactgt
                                                                       177
      <210> 163
      <211> 137
      <212> DNA
      <213> Homo sapien
      <220>
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```
<221> misc_feature
      <222> (1) ... (137)
      <223> n = A, T, C or G
      <400> 163
catttataca gacaggcgtg aagacattca cgacaaaaac gcgaaattct atcccgtgac
                                                                         60
canagaagge agetacgget actectacat cetggegtgg gtggcetteg cetgeacett
                                                                        120
catcagcggc atgatgt
                                                                        137
      <210> 164
      <211> 469
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (469)
      <223> n = A, T, C or G
      <400> 164
cttatcacaa tgaatgttct cctgggcagc gttgtgatct ttgccacctt cgtgacttta
                                                                         60
tgcaatgcat catgctattt catacctaat gagggagttc caggagattc aaccaggaaa
                                                                        120
tgcatggatc tcaaaggaaa caaacaccca ataaactcgg agtggcagac tgacaactgt
                                                                        180
gagacatgca cttgctacga aacagaaatt tcatgttgca cccttgtttc tacacctgtg
                                                                        240
ggttatgaca aagacaactg ccaaagaatc ttcaagaagg aggactgcaa gtatatcgtg
                                                                        300
gtggagaaga aggacccaaa aaagacctgt tctgtcagtg aatggataat ctaatgtgct
                                                                        360
totagtagge acagggetee caggecagge eteattetee tetggeetet aatagteaat
                                                                        420
gattgtgtag ccatgcctat cagtaaqaag atntttgagc aaacacttt
                                                                        469
      <210> 165
     <211> 195
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(195)
      <223> n = A, T, C or G
      <400> 165
acagtttttt atanatatcg acattgccgg cacttgtgtt cagtttcata aagctggtgg
                                                                         60
atcogctgtc atccactatt ccttggctag agtaaaaatt attcttatag cccatgtccc
                                                                        120
                                                                        180
tgcaggccgc.ccgcccgtag ttctcgttcc agtcgtcttg gcacacaggg tgccaggact
tcctctgaga tgagt
                                                                        195
      <210> 166
      <211> 383
      <212> DNA
      <213> Homo sapien
     <220>
      <221> misc_feature
      <222> (1)...(383)
      <223> n = A, T, C or G
      <400> 166
acatettagt agtgtggeae ateaggggge cateagggte acagteacte atageetege
                                                                         60
cgaggtcgga gtccacacca ccggtgtagg tgtgctcaat cttgggcttg gcgcccacct
                                                                        120
ttqqaqaaqq qatatqctqc acacacatqt ccacaaaqcc tqtqaactcq ccaaaqaatt
                                                                        180
                                                                        240
tttgcagacc agcctgagca aggggcggat gttcagcttc agctcctcct tcgtcaggtg
                                                                        300
gatgccaacc tcgtctangg tccgtgggaa gctggtgtcc acntcaccta caacctgggc
gangatetta taaagagget eenagataaa etecaegaaa ettetetggg agetgetagt
                                                                        360
```

```
nggggccttt ttggtgaact ttc
                                                                        383
      <210> 167
      <211> 247
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (247)
      <223> n = A, T, C or G
      <400> 167
acagagecag acettggeca taaatgaane agagattaag actaaacece aagteganat
tggagcagaa actggagcaa gaagtgggcc tggggctgaa gtagagacca aggccactgc
                                                                        120
tatanccata cacagageca acteteagge caaggenatg gttggggeag anecagagae
                                                                        180
tcaatctgan tccaaagtgg tggctggaac actggtcatg acanaggcag tgactctgac
                                                                        240
tgangtc
                                                                        247
      <210> 168
      <211> 273
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (273)
      <223> n = A, T, C or G
      <400> 168
acttctaagt tttctagaag tggaaggatt gtantcatcc tgaaaatggg tttacttcaa
                                                                         60
aatccctcan cettgttett cacnactgte tatactgana gtgtcatgtt tecacaaagg
                                                                        120
gctgacacct gagcctgnat tttcactcat ccctgagaag ccctttccag tagggtgggc
                                                                        180
aattoccaac ttocttgcca caagettocc aggetttotc coctggaaaa ctccagettg
                                                                        240
agtcccagat acactcatgg gctgccctgg gca
                                                                        273
      <210> 169
      <211> 431
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (431)
      <223> n = A, T, C or G
      <400> 169
acagcettgg cttccccaaa ctccacagte teagtgeaga aagateatet tecageagte
                                                                         60
agetcagace agggtcaaag gatgtgacat caacagttte tggtttcaga acaggtteta
                                                                        120
ctactgicaa atgacccccc atacttcctc aaaggctgtg gtaagttttg cacaggtgag
                                                                        180
ggcagcagaa agggggtant tactgatgga caccatcttc tctqtatact ccacactgac
                                                                        240
cttgccatgg gcaaaggccc ctaccacaaa aacaatagga tcactgctgg gcaccagctc
                                                                        300
acgcacatca ctgacaaccg ggatggaaaa agaantgcca actttcatac atccaactgg
                                                                        360
aaagtgatet gatactggat tettaattae etteaaaage ttetggggge cateagetge
                                                                        420
tcgaacactg a
                                                                        431
      <210> 170
      <211> 266
      <212> DNA
      <213> Homo sapien
     <220>
```

```
<221> misc_feature
       <222> (1) ... (266)
       <223> n = A, T, C or G
       <400> 170
acctgtgggc tgggctgtta tgcctgtgcc ggctgctgaa agggagttca gaggtggagc
                                                                         60
 tcaaggaget etgeaggeat tttgecaane etetecanag canagggage aacetacaet
                                                                        120
ccccgctaga aagacaccag attggagtcc tgggaggggg agttggggtg ggcatttgat
                                                                        180
gtatacttgt cacctgaatg aangagccag agaggaanga gacgaanatg anattggcct
                                                                        240
tcaaagctag gggtctggca ggtgga
      <210> 171
      <211> 1248
       <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (1248)
      <223> n = A, T, C or G
      <400> 171
ggcagccaaa tcataaacgg cgaggactgc agcccgcact cgcagccctg gcaggcggca
                                                                         60
ctggtcatgg aaaacgaatt gttctgctcg ggcgtcctgg tgcatccqca gtqqqtqctq
                                                                        120
teageegeae actgttteea gaagtgagtg cagageteet acaccategg getgggeetg
                                                                        180
cacagtettg aggeegacca agageeaggg ageeagatgg tggaggeeag ceteteegta
                                                                        240
eggeacecag agtacaacag accettgete getaacgace teatgeteat caagttggae
                                                                        300
gaatccgtgt ccgagtctga caccatccgg agcatcagca ttgcttcgca gtgccctacc
                                                                        360
geggggaact cttgcctcgt ttctggctgg ggtctgctgg cgaacggcag aatgcctacc gtgctgcagt gcgtgaacgt gtcggtggtg tctgaggagg tctgcagtaa gctctatgac
                                                                        420
                                                                        480
ccgctgtacc accccagcat gttctgcgcc ggcggagggc aagaccagaa ggactcctgc
                                                                       540
aacggtgact ctggggggcc cctgatctgc aacgggtact tgcaqqqcct tgtqtctttc
                                                                        600
ggaaaagccc cgtgtggcca agttggcgtg ccaggtgtct acaccaacct ctgcaaattc
                                                                        660
actgagtgga tagagaaaac cgtccaggcc agttaactct ggggactggg aacccatgaa
                                                                       720
attgaccccc aaatacatcc tgcggaagga attcaggaat atctqttccc agcccctcct
                                                                       780
ccctcaggcc caggagtcca ggcccccagc ccctcctccc tcaaaccaag ggtacagatc
                                                                       840
cecageceet ecteecteag acceaggagt ceagaceee eageceetee teecteagae
                                                                       900
ccaggagtcc agcccctcct ccctcagacc caggagtcca gaccccccag cccttctcc
                                                                       960
ctcagaccca ggggtccagg cccccaaccc ctcctccctc agactcagag gtccaagccc
                                                                      1020
ccaaccente attecccaga cccagaggte caggteccag ccctentee etcaqaccca
                                                                      1080
geggteeaat gecaectaga etnteeetgt acacagtgee eeettgtgge aegttgaece
                                                                      1140
aaccttacca gttggttttt catttttngt ccctttcccc tagatccaga aataaagttt
                                                                      1200
1248
      <210> 172
      <211> 159
      <212> PRT
      <213> Homo sapien
      <220>
      <221> VARIANT
      <222> (1)...(159)
      <223> Xaa = Any Amino Acid
      <400> 172
Met Val Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro
1
                5
                                    10
Leu Leu Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser
                                25
Glu Ser Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr
        35
                40
                                                45
Ala Gly Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly
```

الحاسمين المحجان

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```
55
    50
                                             60
Arg Met Pro Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu
                    70
                                        75
Glu Val Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe
                85
                                    90
Cys Ala Gly Gly Gln Xaa Gln Xaa Asp Ser Cys Asn Gly Asp Ser
            100
                                105
                                                     110
Gly Gly Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe
                            120
                                                 125
Gly Lys Ala Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn
                        135
                                            140
Leu Cys Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser
                    150
                                         155
      <210> 173
      <211> 1265
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (1265)
      <223> n = A, T, C or G
      <400> 173
ggcagcccgc actcgcagcc ctggcaggcg gcactggtca tggaaaacga attgttctgc
                                                                        60
                                                                       120
tegggegtee tggtgeatee geagtgggtg etgteageeg caeactgttt ceagaactee
tacaccateg ggctgggcct gcacagtett gaggccgace aagagccagg gagccagatg
                                                                       180
gtggaggcca gcctctccgt acggcaccca gagtacaaca gacccttgct cgctaacgac
                                                                       240
ctcatgctca tcaagttgga cgaatccgtg tccgagtctg acaccatccg gagcatcagc
                                                                       300
attgettege agtgeeetae egeggggaae tettgeeteg tttetggetg gggtetgetg
                                                                       360
gcgaacggtg agctcacggg tgtgtgtctg coctcttcaa ggaggtcctc tgcccagtcg
                                                                       420
cgggggctga cccagagctc tgcgtcccag gcagaatgcc taccgtgctg cagtgcgtga
                                                                       480
acgtgtcggt ggtgtctgag gaggtctgca gtaagctcta tgacccgctg taccacccca
                                                                       540
gcatgttctg cgccggcgga gggcaagacc agaaggactc ctgcaacggt gactctgggg
                                                                       600
ggcccctgat ctgcaacggg tacttgcagg gccttgtgtc tttcggaaaa gccccgtgtg
                                                                       660
gccaagttgg cgtgccaggt gtctacacca acctctgcaa attcactgag tggatagaga
                                                                       720
aaaccgtcca ggccagttaa ctctggggac tgggaaccca tgaaattgac ccccaaatac
                                                                       780
atcctgcgga aggaattcag gaatatctgt tcccagcccc tcctccctca ggcccaggag
                                                                       840
tecaggeeee cageeeetee teeeteaaac caagggtaca gateeeeage eeeteeteee
                                                                       900
teagacecag gagtecagae ececeagece etecteete agacecagga gtecagecee
                                                                       960
tecteentea gacceaggag tecagaceee ecageceete eteceteaga eccaggggtt
                                                                      1020
gaggececca accectecte etteagagte agaggtecaa gececeaace ectegttece
                                                                      1080
cagacccaga ggtnnaggtc ccagccctc ttccntcaga cccagnggtc caatgccacc
                                                                      1140
tagattttcc ctgnacacag tgcccccttg tggnangttg acccaacctt accagttggt
                                                                      1200
ttttcatttt tnqtcccttt cccctagatc cagaaataaa qtttaaqaqa nqnqcaaaaa
                                                                      1260
                                                                      1265
aaaaa
      <210> 174
      <211> 1459
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(1459)
      <223> n = A, T, C or G
      <400> 174
                                                                        60
ggtcagccgc acactgtttc cagaagtgag tgcagagctc ctacaccatc gggctgggcc
tgcacagtet tgaggeegae caagageeag ggageeagat ggtggaggee ageeteteeg
                                                                       120
```

tacggcaccc agagtacaac agacccttgc tegetaacga ceteatgete atcaagttgg

180

```
acgaatccgt gtccgagtct gacaccatcc ggagcatcag cattgcttcg cagtgcccta
                                                                       240
ccgcggggaa ctcttgcctc gtttctggct ggggtctgct ggcgaacggt gagctcacgg
                                                                       300
gtgtgtgtct gccctcttca aggaggtcct ctgcccagtc gcgggggctg acccagagct
                                                                       360
ctgcgtccca ggcagaatgc ctaccgtgct gcagtgcgtg aacgtgtcgg tggtgtctga
                                                                       420
ngaggtetge antaagetet atgacceget gtaccacece ancatgttet gegeeggegg
                                                                       480
                                                                       540
agggcaagac cagaaggact cctgcaacgt gagagagggg aaaggggagg gcaggcgact
                                                                       600
cagggaaggg tggagaaggg ggagacagag acacacaggg ccgcatggcg agatgcagag
atggagagac acacagggag acagtgacaa ctagagagag aaactgagag aaacagagaa
                                                                       660
ataaacacag gaataaagag aagcaaagga agagagaaac agaaacagac atggggaggc
                                                                       720
                                                                       780
agaaacacac acacatagaa atgcagttga ccttccaaca gcatggggcc tgagggcggt
                                                                       840
gacctccacc caatagaaaa teetettata acttttgact ccccaaaaac ctgactagaa
atagcctact gttgacgggg agccttacca ataacataaa tagtcgattt atgcatacgt
                                                                       900
tttatgcatt catgatatac ctttgttgga attttttgat atttctaagc tacacagttc
                                                                       960
                                                                      1020
gtctgtgaat ttttttaaat tgttgcaact ctcctaaaat ttttctgatg tgtttattga
aaaaatccaa gtataagtgg acttgtgcat tcaaaccagg gttgttcaag ggtcaactgt
                                                                      1080
gtacccagag ggaaacagtg acacagattc atagaggtga aacacgaaga gaaacaggaa
                                                                      1140
aaatcaagac totacaaaga ggctgggcag ggtggctcat gcctgtaatc ccagcacttt
                                                                      1200
gggaggcgag gcaggcagat cacttgaggt aaggagttca agaccagcct ggccaaaatg
                                                                      1260
gtgaaatcct gtctgtacta aaaatacaaa agttagctgg atatggtggc aggcgcctgt
                                                                      1320
aatcccagct acttgggagg ctgaggcagg agaattgctt gaatatggga ggcagaggtt
                                                                      1380
gaagtgagtt gagatcacac cactatactc cagctggggc aacagagtaa gactctgtct
                                                                      1440
caaaaaaaa aaaaaaaaa
                                                                      1459
      <210> 175
      <211> 1167
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(1167)
      <223> n = A, T, C or G
      <400> 175
gegeageeet ggeaggegge actggteatg gaaaaegaat tgttetgete gggegteetg
                                                                        60
gtgcatccgc agtgggtgct gtcagccgca cactgtttcc agaactccta caccatcggg
                                                                       120
ctgggcctgc acagtcttga ggccgaccaa gagccaggga gccagatggt ggaggccagc
                                                                       180
ctctccgtac ggcacccaga gtacaacaga ctcttgctcg ctaacgacct catgctcatc
                                                                       240
                                                                       300
aagttggacg aatccgtgtc cgagtctgac accatccgga gcatcagcat tgcttcgcag
tgccctaccg cggggaactc ttgcctcgtn tctggctggg gtctgctggc gaacggcaga
                                                                       360
atgcctaccg tgctgcactg cgtgaacgtg tcggtggtgt ctgaggangt ctgcagtaag
                                                                       420
                                                                       480
ctctatgacc cgctgtacca ccccagcatg ttctgcgccg gcggagggca agaccagaag
gacteetgea aeggtgacte tggggggeee etgatetgea aegggtaett geagggeett
                                                                       540
gtgtctttcg gaaaagcccc gtgtggccaa cttggcgtgc caggtgtcta caccaacctc
                                                                       600
tgcaaattca ctgagtggat agagaaaacc gtccagncca gttaactctg gggactggga
                                                                       660
acccatgaaa ttgaccccca aatacatcct gcggaangaa ttcaggaata tctgttccca
                                                                       720
gecectecte ceteaggee aggagteeag gececagee cetecteet caaaccaagg
                                                                       780
                                                                       840
gtacagatee ceageceete eteceteaga eceaggagte cagaceeece ageceetent
                                                                       900
centcagace caggagteca geceetecte enteagacge aggagtecag accececage
                                                                       960
cententecg teagacecag gggtgeagge ecceaacece tenteentea gagteagagg
tocaagoooc caacoootog ttococagac coagaggtno aggtoccago coctoctoco
                                                                      1020
teagacceag eggteeaatg ceacctagan thteeetgta cacaqtqeec cettqtqqea
                                                                      1080
                                                                      1140
ngttgaccca accttaccag ttggtttttc attttttgtc cctttcccct agatccagaa
ataaagtnta agagaagcgc aaaaaaa
                                                                      1167
      <210> 176
      <211> 205
      <212> PRT
      <213> Homo sapien
```

<220> <221> VARIANT

45

95

160

75

```
<222> (1)...(205)
      <223> Xaa = Any Amino Acid
      <400> 176
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
                                     10
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
                                25
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
        35
                            40
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Leu Leu Leu
                        55
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                85
                                    90
            100
                                105
                            120
```

Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met 110 Pro Thr Val Leu His Cys Val Asn Val Ser Val Val Ser Glu Xaa Val 125 Cys Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala 130 135 140 Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly 150 155 Pro Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys 165 170 175 Ala Pro Cys Gly Gln Leu Gly Val Pro Gly Val Tyr Thr Asn Leu Cys 180 185 Lys Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Xaa Ser

200

<210> 177 <211> 1119 <212> DNA

<213> Homo sapien

<400> 177

gegeactege agecetggea ggeggeactg gteatggaaa aegaattgtt etgeteggge 60 gtectggtge atccgcagtg ggtgctgtca gecgcacact gtttccagaa etectacace atcgggetgg gectgcacag tettgaggee gaccaagage cagggageea gatggtggag 120 180 gecageetet cegtaeggea eccagagtae aacagaeeet tgetegetaa egaceteatg 240 ctcatcaagt tggacqaatc cqtgtccqaq tctgacacca tccgqaqcat caqcattqct 300 360 tegeagtgee etacegeggg gaactettge etegtttetg getggggtet getggegaae gatgctgtga ttgccatcca gtcccagact gtgggaggct gggagtgtga gaagctttcc 420 caaccetgge agggttgtac cattteggea acttecagtg caaggacgte etgetgeate 480 ctcactgggt gctcactact gctcactgca tcacccggaa cactgtgatc aactagccag 540 caccatagtt ctccgaagtc agactatcat gattactgtg ttgactgtgc tgtctattgt 600 660 actaaccatg ccgatgttta ggtgaaatta gcgtcacttg gcctcaacca tcttggtatc cagttateet caetgaattg agattteetg etteagtgte agecatteee acataattte 720 tgacctacaq aqqtgaggga tcatatagct cttcaaggat gctqqtactc ccctcacaaa 780 840 ttcatttctc ctgttgtagt gaaaggtgcg ccctctggag cctcccaggg tgggtgtgca ggtcacaatg atgaatgtat gatcgtgttc ccattaccca aagcctttaa atccctcatg 900 ctcagtacac cagggcaggt ctagcatttc ttcatttagt gtatgctgtc cattcatgca 960 1020 accacctcag gactcctgga ttctctgcct agttgagctc ctgcatgctg cctccttggg gaggtgaggg agagggccca tggttcaatg ggatctgtgc agttgtaaca cattaggtgc 1080 ttaataaaca gaagctgtga tgttaaaaaa aaaaaaaaa 1119

<210> 178 <211> 164 <212> PRT

<213> Homo sapien

```
<220>
      <221> VARIANT
      <222> (1)...(164)
      <223> Xaa = Any Amino Acid
      <400> 178
Met Glu Asn Glu Leu Phe Cys Ser Gly Val Leu Val His Pro Gln Trp
1
                                     10
                                                         15
Val Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu
            20
                                25
                                                     30
Gly Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val
                            40
Glu Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu
                        55
Ala Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser
                                        75
                    70
Asp Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly
                                     90
                                                         95
Asn Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Asp Ala Val
            100
                                105
                                                     110
Ile Ala Ile Gln Ser Xaa Thr Val Gly Gly Trp Glu Cys Glu Lys Leu
                                                 125
        115
                            120
Ser Gln Pro Trp Gln Gly Cys Thr Ile Ser Ala Thr Ser Ser Ala Arg
                        135
                                             140
Thr Ser Cys Cys Ile Leu Thr Gly Cys Ser Leu Leu Thr Ala Ser
Pro Gly Thr Leu
      <210> 179
      <211> 250
      <212> DNA
      <213> Homo sapien
      <400> 179
ctggagtgcc ttggtgtttc aagcccctgc aggaagcaga atgcaccttc tgaggcacct
                                                                        60
ccagctgccc ccggccgggg gatgcgaggc tcggagcacc cttgcccggc tgtgattgct
                                                                        120
                                                                        180
gccaggcact gttcatctca gcttttctgt ccctttgctc ccggcaageg cttctgctga
aagttcatat ctggagcctg atgtcttaac gaataaaggt cccatgctcc acccgaaaaa
                                                                        240
                                                                        250
aaaaaaaaa
      <210> 180
      <211> 202
      <212> DNA
      <213> Homo sapien
      <400> 180
actagtccag tgtggtggaa ttccattgtg ttgggcccaa cacaatggct acctttaaca
                                                                        60
                                                                        120
teacceagae ecegeceetg ecegtgeece acgetgetge taacgacagt atgatgetta
                                                                        180
ctctgctact cggaaactat ttttatgtaa ttaatgtatg ctttcttgtt tataaatgcc
                                                                        202
tgatttaaaa aaaaaaaaaa aa
      <210> 181
      <211> 558
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (558)
      <223> n = A,T,C or G
```

```
<400> 181
tccytttqkt nagqtttkkq aqacamccck aqacctwaan ctqtqtcaca qacttcyngq
                                                                         60
aatgtttagg cagtgctagt aatttcytcg taatgattct qttattactt tectnattet
                                                                        120
ttattcctct ttcttctgaa gattaatgaa gttgaaaatt gaggtggata aatacaaaaa
                                                                        180
ggtagtgtga tagtataagt atctaagtgc agatgaaagt gtgttatata tatccattca
                                                                        240
aaattatgca agttagtaat tactcagggt taactaaatt actttaatat gctgttgaac
                                                                        300
ctactctgtt ccttggctag aaaaaattat aaacaggact ttgttagttt gggaagccaa
                                                                        360
attgataata ttctatgttc taaaagttgg gctatacata aattattaag aaatatggaw
                                                                        420
ttttattccc aggaatatgg kgttcatttt atgaatatta cscrggatag awgtwtgagt
                                                                        480
aaaaycagtt ttggtwaata ygtwaatatg tcmtaaataa acaakgcttt gacttatttc
                                                                        540
caaaaaaaa aaaaaaaa
                                                                        558
      <210> 182
      <211> 479
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (479)
      <223> n = A, T, C or G
      <400> 182
acagggwttk grggatgcta agsccccrga rwtygtttga tccaaccctg gcttwttttc
                                                                         60
agaggggaaa atggggccta gaagttacag mscatytaqy tqqtqcqmtq qcacccctqq
                                                                        120
cstcacacag astcccgagt agetgggact acaggcacac agtcactgaa gcaggccctq
                                                                        180
ttwgcaattc acgttgccac ctccaactta aacattcttc atatgtgatg tccttagtca
                                                                        240
ctaaggttaa actttcccac ccagaaaagg caacttagat aaaatcttag agtactttca
                                                                        300
tactmttcta agtcctcttc cagcctcact kkgagtcctm cytgggggtt gataggaant
                                                                        360
ntctcttggc tttctcaata aartctctat ycatctcatg tttaatttgg tacqcatara
                                                                        420
awtgstgara aaattaaaat gttctggtty mactttaaaa araaaaaaaa aaaaaaaaa
                                                                        479
      <210> 183
      <211> 384
      <212> DNA
      <213> Homo sapien
aggegggage agaagetaaa gecaaageee aagaagagtg geagtgeeag eactggtgee
                                                                        60
agtaccagta ccaataacag tgccagtgcc agtgccagca ccagtggtgg cttcagtgct
                                                                       120
ggtgccagcc tgaccgccac tctcacattt gggctcttcg ctggccttgg tggagctggt
                                                                       180
gccagcacca gtggcagctc tggtgcctgt ggtttctcct acaagtgaga ttttagatat
                                                                       240
tgttaatcet gecagtettt etetteaage eagggtgeat eeteagaaae etaeteaaea
                                                                       300
cagcactcta ggcagccact atcaatcaat tgaagttqac actctqcatt aratctattt
                                                                       360
gccatttcaa aaaaaaaaaa aaaa
                                                                       384
      <210> 184
      <211> 496
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (496)
      <223> n = A, T, C or G
      <400> 184
accgaattgg gaccgctggc ttataagcga tcatgtyynt ccrgtatkac ctcaacqaqc
                                                                        60
agggagatcg agtctatacg ctgaagaaat ttgacccgat gggacaacag acctgctcag
                                                                       120
cccatcctgc teggttetec ccagatgaca aatactetsg acaccgaate accatcaaga
                                                                       180
aacgcttcaa ggtgctcatg acccagcaac cgcgccctgt cctctgaggg tcccttaaac
                                                                       240
tgatgtettt tetgecacet gttaceete ggagaeteeg taaccaaact etteggaetg
                                                                       300
```

```
tgagccctga tgcctttttg ccagccatac tctttggcat ccagtctctc gtggcgattg
                                                                        360
attatgcttg tgtgaggcaa tcatgqtqqc atcacccata aaqqqaacac atttqacttt
                                                                        420
tttttctcat attttaaatt actacmagaw tattwmagaw waaatgawtt gaaaaactst
                                                                        480
taaaaaaaa aaaaaa
                                                                        496
      <210> 185
      <211> 384
      <212> DNA
      <213> Homo sapien
      <400> 185
gctggtagcc tatggcgkgg cccacggagg ggctcctgag gccacggrac agtgacttcc
                                                                         60
caagtatcyt gcgcsgcgtc ttctaccgtc cctacctgca gatcttcggg cagattcccc
                                                                        120
aggaggacat ggacgtggcc ctcatggagc acagcaactg ytcgtcggag cccqqcttct
                                                                        180
gggcacaccc teetggggee caggeggea cetgegtete ceagtatgee aactggetgg
                                                                        240
tggtgctgct cctcgtcatc ttcctgctcg tggccaacat cctgctggtc aacttgctca
                                                                        300
ttgccatgtt cagttacaca ttcggcaaag tacagggcaa cagcgatctc tactgggaag
                                                                        360
gcgcagcgtt accgcctcat ccgg
                                                                        384
      <210> 186
      <211> 577
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (577)
      <223> n = A, T, C or G
      <400> 186
gagttagete etceacaace ttgatgaggt egtetgeagt ggeetetege tteatacege
                                                                        60
tnccatcgtc atactgtagg tttgccacca cytcctggca tcttggggcg gcntaatatt
                                                                       120
ccaggaaact ctcaatcaag tcaccgtcga tgaaacctgt gggctggttc tgtcttccgc
                                                                       180
teggtgtgaa aggatetece agaaggagtg etegatette eccacaettt tgatgaettt
                                                                       240
attgagtcga ttctgcatgt ccagcaggag gttgtaccag ctctctgaca gtgaggtcac
                                                                       300
cagecetate atgeogttga megtgeogaa garcacegag cettgtgtgg gggkkgaagt
                                                                       360
ctcacccaga ttctgcatta ccagagagcc gtggcaaaag acattgacaa actcgcccag
                                                                       420
gtggaaaaag amcamctcct ggargtgctn gccgctcctc gtcmgttggt ggcagcgctw
                                                                       480
tccttttgac acacaaacaa gttaaaggca ttttcagccc ccagaaantt gtcatcatcc
                                                                       540
                                                                       577
aagatntcgc acagcactna tccagttggg attaaat
      <210> 187
      <211> 534
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(534)
      <223> n = A, T, C or G
aacatcttcc tgtataatgc tgtgtaatat cgatccgatn ttgtctgstg agaatycatw
                                                                        60
actkggaaaa gmaacattaa agcctggaca ctggtattaa aattcacaat atgcaacact
                                                                       120
ttaaacagtg tgtcaatctg ctcccyynac tttgtcatca ccagtctggg aakaagggta
                                                                       180
tgccctattc acacctgtta aaagggcgct aagcattttt gattcaacat ctttttttt
                                                                       240
gacacaagtc cgaaaaaagc aaaagtaaac agttatyaat ttgttagcca attcactttc
                                                                       300
ttcatqqqac agagccatyt gatttaaaaa gcaaattgca taatattgag cttygggagc
                                                                       360
tgatatttga geggaagagt ageettteta etteaceaga cacaacteee ttteatattg
                                                                       420
                                                                       480
ggatgttnac naaagtwatg tctctwacag atgggatgct tttgtggcaa ttctgttctg
aggatetece agtttattta ceaettgeae aagaaggegt tttetteete agge
                                                                       534
```

```
<210> 188
       <211> 761
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (761)
       <223> n = A, T, C or G
      <400> 188
aqaaaccaqt atctctnaaa acaacctctc ataccttgtg gacctaattt tgtgtgcgtg
tgtgtgtgcg cgcatattat ataqacaqgc acatcttttt tacttttgta aaagcttatg
                                                                        120
cctctttggt atctatatct gtgaaagttt taatgatctg ccataatgtc ttggggacct
                                                                        180
ttgtcttctg tgtaaatggt actagagaaa acacctatnt tatgagtcaa tctagttngt
                                                                        240
tttattcgac atgaaggaaa tttccagatn acaacactna caaactctcc ctkgackarg
                                                                        300
ggggacaaag aaaagcaaaa ctgamcataa raaacaatwa cctggtgaga arttgcataa
                                                                       360
acaqaaatwr ggtagtatat tgaarnacag catcattaaa rmgttwtktt wttctccctt
                                                                        420
gcaaaaaaca tgtacngact tcccgttgag taatgccaag ttgtttttt tatnataaaa
                                                                        480
cttgcccttc attacatgtt tnaaagtggt gtggtgggcc aaaatattga aatgatggaa
                                                                       540
ctgactgata aagctgtaca aataagcagt gtgcctaaca agcaacacag taatgttgac
                                                                        600
atgettaatt cacaaatget aattteatta taaatgtttg etaaaataca etttgaacta
                                                                       660
tttttctgtn ttcccagage tgagatntta gattttatgt agtatnaagt gaaaaantac
                                                                       720
gaaaataata acattgaaga aaaananaaa aaanaaaaaa a
                                                                       761
      <210> 189
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(482)
      <223> n = A, T, C or G
      <400> 189
ttttttttt tttgccgatn ctactatttt attgcaggan gtgggggtgt atgcaccqca
                                                                        60
caccggggct atnagaagca agaaggaagg agggaggca cagccccttg ctgagcaaca
                                                                       120
aagccgcctg ctgccttctc tgtctgtctc ctggtgcagg cacatgggga gaccttcccc
                                                                       180
aaggcagggg ccaccagtcc aggggtggga atacaggggg tgggangtgt gcataagaag
                                                                       240
tgataggcac aggccacccg gtacagaccc ctcggctcct gacaggtnga tttcgaccag
                                                                       300
gtcattgtgc cctgcccagg cacagcgtan atctggaaaa gacagaatgc tttccttttc
                                                                       360
aaatttggct ngtcatngaa ngggcanttt tccaanttng gctnggtctt ggtacncttg
                                                                       420
gtteggeeca geteenegte caaaaantat teaccennet cenaattget tgenggneec
                                                                       480
CC
                                                                       482
      <210> 190
    · <211> 471
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(471)
      <223> n = A, T, C or G
      <400> 190
tttttttt ttttaaaaca gttttcaca acaaaattta ttagaagaat agtggttttg
                                                                        60
aaaactctcg catccagtga gaactaccat acaccacatt acagctngga atgtnctcca
                                                                       120
aatgtctggt caaatgatac aatggaacca ttcaatctta cacatgcacg aaagaacaag
                                                                       180
cgcttttgac atacaatgca caaaaaaaaa agggggggg gaccacatgg attaaaattt
                                                                       240
taagtactca tcacatacat taagacacag ttctagtcca gtcnaaaatc agaactgcnt
                                                                       300
```

```
tgaaaaattt catgtatgca atccaaccaa agaacttnat tggtgatcat gantnctcta
                                                                        360
ctacatenae ettgateatt geeaggaaen aaaagttnaa aneaenengt acaaaaanaa
                                                                        420
totgtaattn anttoaacot cogtacngaa aaatnttnnt tatacactoo c
                                                                        471
      <210> 191
      <211> 402
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (402)
      <223> n = A, T, C or G
      <400> 191
gagggattga aggtetgtte tastgteggm etgtteagee accaacteta acaagttget
                                                                         60
gtcttccact cactgtctgt aagcttttta acccagacwg tatcttcata aatagaacaa
                                                                        120
attetteace agteacatet tetaggacet tittggatte agttagtata agetetteea
                                                                        240
cttcctttgt taagacttca tctggtaaag tcttaagttt tgtagaaagg aattyaattg
ctcgttctct aacaatgtcc tctccttgaa gtatttggct gaacaaccca cctaaagtcc
                                                                        300
ctttgtgcat ccattttaaa tatacttaat agggcattgk tncactaggt taaattctgc
                                                                        360
aagagtcatc tgtctgcaaa agttgcgtta gtatatctgc ca
                                                                        402
      <210> 192
      <211> 601
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(601)
      <223> n = A, T, C or G
      <400> 192
gageteggat ecaataatet ttgtetgagg geageacaea tatneagtge eatggnaact
                                                                         60
                                                                        120
ggtctacccc acatgggagc agcatgccgt agntatataa ggtcattccc tgagtcagac
atgcytyttt gaytaccgtg tgccaagtgc tggtgattct yaacacacyt ccatcccgyt
                                                                        180
cttttgtgga aaaactggca cttktctgga actagcarga catcacttac aaattcaccc
                                                                        240
acgagacact tgaaaggtgt aacaaagcga ytcttgcatt gctttttgtc cctccggcac
                                                                        300
cagtigicaa tactaacccg ciggitigcc tocatcacat tigigatcig tagcicigga
                                                                        360
tacatctcct gacagtactg aagaacttct tcttttgttt caaaagcarc tcttggtgcc
                                                                        420
tgttggatca ggttcccatt tcccagtcyg aatgttcaca tggcatattt wacttcccac
                                                                        480
aaaacattgc gatttgaggc tcagcaacag caaatcctgt tccggcattg gctgcaagag
                                                                        540
cctcgatgta gccggccagc gccaaggcag gcgccgtgag ccccaccagc agcagaagca
                                                                        600
                                                                        601
      <210> 193
      <211> 608
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(608)
      <223> n = A, T, C \text{ or } G
      <400> 193
atacagecca nateceacea egaagatgeg ettgttgaet gagaacetga tgeggteaet
                                                                        60
ggtcccgctg tagccccagc gactctccac ctgctggaag cggttgatgc tgcactcytt
                                                                        120
cccaacgcag gcagmagcgg gsccggtcaa tgaactccay tcgtggcttg gggtkgacgg
                                                                       180
tkaagtgcag gaagaggctg accacctcgc ggtccaccag gatgcccgac tgtgcgggac
                                                                       240
ctgcagcgaa actcctcgat ggtcatgagc gggaagcgaa tgaggcccag ggccttgccc
                                                                       300
```

agaacettee geetgttete tggegteaee tgeagetget ge gaecagegga caaacggert tgaacageeg caceteaegg at caggammgse accagegtgt ecaggteaat gteggtgaag ec etgeagtgtt tttgtegatg tteteeagge acaggetgge ea gtegegeetg egtgageage atgaaggegt tgteggeteg ea caegeaat	tgcccagtg tgtcgcgctc 420 cctccgcgg gtratggcgt 480 agctgcggt tcatcgaaga 540
<210> 194 <211> 392 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(392) <223> n = A,T,C or G	
<pre>&lt;400&gt; 194 gaacggctgg accttgcctc gcattgtgct tgctggcagg ga ccagtccgag cagccccaga ccgctgccgc ccgaagctaa gc tccgcctcaa tgcagaacca gtagtgggag cactgtgttt ag tttgatttta cttgggaatt tcctctgtta tatagctttt cc aacaacaaca aaataacatg tttgcctgtt aagttgtata aa taaagaaaat attactgtta catatactgc ttgcaatttc tg aaataaatat agttattaaa ggttgtcant cc</pre>	cctgcctct ggccttcccc 120 gagttaaga gtgaacactg 180 ccaatgcta atttccaaac 240 aagtaggtg attctgtatt 300
<210> 195 <211> 502 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(502) <223> n = A,T,C or G	
<pre>&lt;400&gt; 195 ccsttkgagg ggtkaggkyc cagttyccga gtggaagaaa ca ccgagctgag gcagatgttc ccacagtgac ccccagagcc st cctcncaagg aaagaccacs ttctggggac atgggctgga gg aagggaaggc cccattccgg ggstgttccc cgaggaggaa gg ccccasgagg aagaggccct gagtcctggg atcagacacc cc caaatgcaag ctcaccaagg tcccctctca gtccccttcc st gscscacacc cacccagagc acgccacccg ccatggggar tg gcarcgtgga catctngtcc cagaaggggg cagaatctcc aa gctnanaaaa aaaaanaaaa aa</pre>	tgggstata gtytctgacc 120 ggcaggacc tagaggcacc 180 ggaaggggc tctgtgtgcc 240 cttcacgtg tatccccaca 300 tacaccctg amcggccact 360 gtgctcaag gartcgcngg 420
<210> 196 <211> 665 <212> DNA <213> Homo sapien	
<220> <221> misc_feature <222> (1)(665) <223> n = A,T,C or G	
<pre>&lt;400&gt; 196 ggttacttgg tttcattgcc accacttagt ggatgtcatt ta cctctggaag ccttgcgcag agcggacttt gtaattgttg ga wagctgtttk gagttgatts gcaccactgc acccacaact tc actwatttat tatcttgtga aaagtataac aatgaaaatt tt</pre>	agaataact gctgaatttt 120 caatatgaa aacyawttga 180

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aagtatgatg aaaagcaawa gatatatatt cttttattat gttaaattat gattgccatt
                                                                         300 -
 attaatcggc aaaatgtgga gtgtatgttc ttttcacagt aatatatgcc ttttgtaact
                                                                        360
 tcacttggtt attttattgt aaatgartta caaaattctt aatttaagar aatggtatgt
                                                                         420
 watatttatt tcattaattt ctttcctkgt ttacgtwaat tttgaaaaga wtgcatgatt
                                                                         480
 tottgacaga aatcgatctt gatgctgtgg aagtagtttg acccacatcc ctatgagttt
                                                                         540
 ttcttagaat gtataaaggt tgtagcccat cnaacttcaa agaaaaaaat gaccacatac
                                                                         600
 tttgcaatca ggctgaaatg tggcatgctn ttctaattcc aactttataa actagcaaan
                                                                        660
 aagtg
                                                                         665
       <210> 197
       <211> 492
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (492)
       <223> n = A, T, C or G
       <400> 197
 ttttnttttt tttttttgc aggaaggatt ccatttattg tggatgcatt ttcacaatat
                                                                         60
 atgtttattg gagcgatcca ttatcagtga aaagtatcaa gtgtttataa natttttagg
                                                                        120
 aaggcagatt cacagaacat gctngtenge ttgcagtttt acctcgtana gatnacagag
                                                                        180
aattatagtc naaccagtaa acnaggaatt tacttttcaa aagattaaat ccaaactgaa
                                                                        240
caaaattota cootgaaact tactocatoo aaatattgga ataanagtoa goagtgatao
                                                                        300
attetettet gaactttaga ttttetagaa aaatatgtaa tagtgateag gaagagetet
                                                                        360
tgttcaaaag tacaacnaag caatgttccc ttaccatagg ccttaattca aactttgatc
                                                                        420
cattleacte ceateacggg agteaatget acctgggaca cttgtatttt gtteatnetg
                                                                        480
ancntggctt aa
                                                                        492
      <210> 198
      <211> 478
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(478)
      <223> n = A, T, C or G
      <400> 198
tttnttttgn atttcantct gtannaanta ttttcattat gtttattana aaaatatnaa
                                                                         60
tgtntccacn acaaatcatn ttacntnagt aagaggccan ctacattgta caacatacac
                                                                        120
tgagtatatt ttgaaaagga caagtttaaa gtanacncat attgccganc atancacatt
                                                                        180
tatacatggc ttgattgata tttagcacag canaaactga gtgagttacc agaaanaaat
                                                                        240
natatatgtc aatcngattt aagatacaaa acagatccta tggtacatan catcntgtag
                                                                        300
gagttgtggc tttatgttta ctgaaagtca atgcagttcc tgtacaaaga gatggccgta
                                                                        360
agcattotag tacctotact coatggttaa gaatcgtaca cttatgttta catatgtnca
                                                                        420
gggtaagaat tgtgttaagt naanttatgg agaggtccan gagaaaaatt tgatncaa
                                                                        478
      <210> 199
      <211> 482
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(482)
      <223> n = A,T,C or G
      <400> 199
agtgacttgt cctccaacaa aaccccttga tcaagtttgt ggcactgaca atcagaccta
                                                                        60
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120
tgctagttcc tgtcatctat tcqctactaa atqcagactq qaggggacca aaaaggggca
tcaactccag ctggattatt ttggagcctg caaatctatt cctacttgta cggactttga
                                                                      180
agtgattcag tttcctctac ggatgagaga ctggctcaag aatatcctca tgcagcttta
                                                                      240
tqaaqccnac tctgaacacg ctggttatct nagatgagaa ncagagaaat aaagtcnaga
                                                                      300
aaatttacct ggangaaaag aggetttngg etggggacca teccattgaa eettetetta
                                                                      360
anggacttta agaanaaact accacatgtn tgtngtatcc tggtgccngg ccgtttantg
                                                                      420
aacningach neaccetthi ggaatanant ettgaengen teetgaacti geteetetge
                                                                      480
                                                                      482
      <210> 200
      <211> 270
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (270)
      <223> n = A, T, C or G
      <400> 200
cqqccqcaaq tqcaactcca gctggggccg tgcggacgaa gattctgcca gcagttggtc
                                                                       60
cgactgcgac gacggcggcg gcgacagtcg caggtgcagc gcggggcgcct ggggtcttgc
                                                                      120
aaggetgage tgacgecgca gaggtegtgt cacgteccae gacettgaeg eegtegggga
                                                                      180
                                                                      240
cagecggaac agageceggt gaangeggga ggeetegggg ageeeetegg gaagggegge
                                                                      270
ccgagagata cgcaggtgca ggtggccgcc
      <210> 201
      <211> 419
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (419)
      <223> n = A, T, C or G
      <400> 201
ttttttttt ttttggaatc tactgcgagc acagcaggtc agcaacaagt ttattttgca
                                                                       60
gctagcaagg taacagggta gggcatggtt acatgttcag gtcaacttcc tttgtcqtqq
                                                                      120
                                                                      180
ttgattggtt tgtctttatg ggggcggggt ggggtagggg aaancgaagc anaantaaca
tggagtgggt gcaccctccc tgtagaacct ggttacnaaa gcttggggca gttcacctgg
                                                                      240
                                                                      300
totgtgaccg toattttctt gacatcaatg ttattagaag toaggatato ttttagagag
tccactqtnt ctqqaqqqag attaqqqttt cttqccaana tccaancaaa atccacntga
                                                                      360
aaaagttgga tgatncangt acngaatacc ganggcatan ttctcatant cggtggcca
                                                                      419
      <210> 202
      <211> 509
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (509)
      <223> n = A, T, C or G
      <400> 202
                                                                       60
tttnttttt tttttttt tttttttt tttttttt
tggcacttaa tccatttta tttcaaaatg tctacaaant ttnaatncnc cattatacng
                                                                      120
gtnattttnc aaaatctaaa nnttattcaa atntnagcca aantccttac ncaaatnnaa
                                                                      180
tacnoncaaa aatcaaaaat atacntntot ttoagcaaac ttngttacat aaattaaaaa
                                                                      240
aatatatacg gctggtgttt tcaaagtaca attatcttaa cactgcaaac atntttnnaa
                                                                       300
qqaactaaaa taaaaaaaaa cactnoogca aaggttaaag ggaacaacaa attontttta
                                                                       360
```

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caacancnnc nattataaaa atcatatctc aaatcttagg ggaatatata cttcacacng
                                                                              420
ggatcttaac ttttactnca ctttgtttat ttttttanaa ccattgtntt qqqcccaaca
                                                                              480
caatggnaat nccnccncnc tggactagt
                                                                              509
       <210> 203 <211> 583
       <212> DNA
       <213> Homo sapien
       <220>
       <221> misc_feature
       <222> (1) ... (583)
       <223> n = A, T, C or G
       <400> 203
ttttttttt tttttttga cocccctctt ataaaaaaca agttaccatt ttattttact
                                                                               60
tacacatatt tattttataa ttggtattag atattcaaaa ggcagctttt aaaatcaaac taaatggaaa ctgccttaga tacataattc ttaggaatta gcttaaaatc tgcctaaagt
                                                                              120
                                                                              180
gaaaatette tetagetett ttgactgtaa attittgact ettgtaaaac atecaaatte
                                                                              240
attititetty tettiaaaat tatetaatet tieeattitt teeetattee aagteaatti
                                                                              300
gettetetag ceteatttee tagetettat etaetattag taagtggett tttteetaaa
                                                                              360
agggaaaaca ggaagagana atggcacaca aaacaaacat tttatattca tatttctacc
                                                                              420
tacgttaata aaatagcatt ttgtgaagcc agctcaaaag aaggcttaga tccttttatg
                                                                              480
tocattttag toactaaacg atatonaaag tgocagaatg caaaaggttt gtgaacattt
                                                                              540
attcaaaagc taatataaga tatttcacat actcatcttt ctq
                                                                              583
       <210> 204
       <211> 589
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      · <222> (1) ... (589)
      <223> n = A, T, C or G
      <400> 204
ttttttttt tttttttt tttttttctc ttctttttt ttganaatga ggatcgagtt
                                                                               60
tttcactctc tagatagggc atgaagaaaa ctcatctttc cagctttaaa ataacaatca
                                                                              120
aatctcttat gctatatcat attttaagtt aaactaatga gtcactggct tatcttctcc
                                                                              180
tgaaggaaat ctgttcattc ttctcattca tatagttata tcaagtacta ccttgcatat
                                                                              240
tgagaggttt ttcttctcta tttacacata tatttccatg tgaatttgta tcaaaccttt
                                                                              300
attttcatgc aaactagaaa ataatqtntt cttttqcata aqaqaaqaqa acaatatnaq
                                                                              360
cattacaaaa ctgctcaaat tgtttgttaa gnttatccat tataattagt tnggcaggag
                                                                              420
ctaatacaaa tcacatttac ngacnagcaa taataaaact gaagtaccag ttaaatatcc aaaataatta aaggaacatt tttagcctgg gtataattag ctaattcact ttacaagcat
                                                                              480
                                                                              540
ttattnagaa tgaattcaca tgttattatt contagocca acacaatgg
                                                                              589
      <210> 205
      <211> 545
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      \langle 222 \rangle (1)...(545)
\langle 223 \rangle n = A,T,C or G
      <400> 205
tttttntttt ttttttcagt aataatcaga acaatattta tttttatatt taaaattcat
                                                                               60
agaaaagtgc cttacattta ataaaagttt gtttctcaaa gtgatcagag gaattagata
                                                                              120
tngtcttgaa caccaatatt aatttgagga aaatacacca aaatacatta agtaaattat
```

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ttaaqatcat agagcttgta agtgaaaaga taaaatttga cctcagaaac tctgagcatt
                                                                        240
aaaaatccac tattagcaaa taaattacta tggacttctt gctttaattt tgtgatgaat
                                                                        300
atggggtgtc actggtaaac caacacattc tgaaggatac attacttagt gatagattct
                                                                        360
tatgtacttt gctanatnac gtggatatga gttgacaagt ttctctttct tcaatctttt
                                                                        420
aaggggenga ngaaatgagg aagaaaagaa aaggattacg catactgtte tttetatngg
                                                                        480
aaqqattaqa tatqtttcct ttqccaatat taaaaaaata ataatqttta ctactaqtga
                                                                        540
                                                                        545
aaccc
      <210> 206
      <211> 487
      <212> DNA
      <213> Homo sapien
      <221> misc feature
      <222> (1) ... (487)
      <223> n = A, T, C or G
      <400> 206
ttttttttt ttttttagtc aagtttctna tttttattat aattaaagtc ttggtcattt
                                                                         60
catttattag ctctgcaact tacatattta aattaaagaa acgttnttag acaactgtna
                                                                        120
caatttataa atgtaaggtg ccattattga gtanatatat tcctccaaga gtggatgtgt
                                                                        180
cccttctccc accaactaat qaancaqcaa cattaqttta attttattaq tagatnatac
                                                                        240
actgctgcaa acgctaattc tcttctccat ccccatgtng atattgtgta tatgtgtgag
                                                                        300
ttgqtnaqaa tqcatcanca atctnacaat caacaqcaag atgaagctag gcntgggctt
                                                                        360
teggtgaaaa tagaetgtgt etgtetgaat caaatgatet gaeetateet eggtggeaag
                                                                        420
aactettega accepttect caaaggenge tgccacattt gtggentetn ttgcacttgt
                                                                        480
ttcaaaa
                                                                        487
      <210> 207
      <211> 332
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(332)
      <223> n = A,T,C or G
      <400> 207
tqaattqqct aaaaqactqc atttttanaa ctaqcaactc ttatttcttt cctttaaaaa
                                                                         60
tacatagcat taaatcccaa atcctattta aagacctgac agcttgagaa ggtcactact
                                                                        120
                                                                        180
gcatttatag gaccttctgg tggttctgct gttacntttg aantctgaca atccttgana
atotttgcat gcagaggagg taaaaggtat tggattttca cagaggaana acacagcgca
                                                                        240
gaaatgaagg ggccaggctt actgagcttg tccactggag ggctcatggg tgggacatgg
                                                                        300
aaaagaaqqc aqcctaggcc ctggggaqcc ca
                                                                        332
    · <210> 208
      <211> 524
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (524)
      <223> n = A, T, C or G
agggcgtggt gcggagggcg ttactgtttt gtctcagtaa caataaatac aaaaagactg
                                                                        60
gttgtgttcc ggccccatcc aaccacgaag ttgatttctc ttgtgtgcag agtgactgat
                                                                        120
tttaaaggac atggagcttg tcacaatgtc acaatgtcac agtgtgaagg gcacactcac
                                                                       180
tcccgcgtga ttcacattta gcaaccaaca atagctcatg agtccatact tgtaaatact
                                                                       240
```

```
tttggcagaa tacttnttga aacttgcaga.tgataactaa gatccaagat atttcccaaa
                                                                         300
gtaaatagaa gtgggtcata atattaatta cctgttcaca tcagcttcca tttacaaqtc
                                                                         360
atgageccag acactgacat caaactaage ceaettagae teetcaceae cagtetgtee
                                                                         420
tgtcatcaga caggaggctg tcaccttgac caaattctca ccagtcaatc atctatccaa
                                                                         480
aaaccattac ctgatccact tccggtaatg caccaccttg gtga
                                                                         524
       <210> 209
       <211> 159
       <212> DNA
       <213> Homo sapien
       <400> 209
gggtgaggaa atccagagtt gccatggaga aaattccagt gtcagcattc ttgctccttg
                                                                          60
tggccctctc ctacactctg gccagagata ccacagtcaa acctggagcc aaaaaggaca
                                                                         120
caaaggactc tcgacccaaa ctgccccaga ccctctcca
                                                                         159
       <210> 210
      <211> 256
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1) ... (256)
      <223> n = A, T, C or G
      <400> 210
actocotggo agacaaaggo agaggagaga gototgttag ttotgtgttq ttqaactqoo
                                                                          60
actgaatttc tttccacttg gactattaca tgccanttga gggactaatg gaaaaacqta
                                                                         120
tggggagatt ttanccaatt tangtntgta aatggggaga ctggggcagg cgggagagat
                                                                         180
ttgcagggtg naaatgggan ggctggtttg ttanatgaac agggacatag gaggtaggca
                                                                         240
ccaggatgct aaatca
                                                                         256
      <210> 211
      <211> 264
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
      <222> (1)...(264)
      <223> n = A, T, C or G
      <400> 211
acattgtttt tttgagataa agcattgaga gagctctcct taacgtgaca caatggaagg
                                                                         60
actggaacac atacccacat ctttgttctg agggataatt ttctgataaa gtcttgctgt
                                                                        120
atattcaagc acatatgtta tatattattc agttccatgt ttatagccta gttaaggaga
                                                                        180
ggggagatac attengaaag aggactgaaa gaaatactca agtnggaaaa cagaaaaaga
                                                                        240
aaaaaaggag caaatgagaa gcct
                                                                        264
      <210> 212
      <211> 328
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      \langle 223 \rangle n = A, T, C or G
      <400> 212
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                                                                         60
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ggatttaatg ttgtctcagc ttgggcactt cagttaggac ctaaggatgc cagccggcag
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gtttatatat gcagcaacaa tattcaagcg cgacaacagg ttattgaact tgcccqccag
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ttnaatttca ttcccattga cttgggatcc ttatcatcag ccagagagat tgaaaattta
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cccctacnac tctttactct ctgganaggg ccagtggtgg tagctataag cttggccaca
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ttttttttc ctttattcct ttgtcaga
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      <211> 250
      <212> DNA
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      <220>
      <221> misc feature
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      <223> n = A, T, C or G
      <400> 213
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taaagcattg ctcactgaag ggatagaagt gactgccagg agggaaagta agccaaggct
                                                                        120
cattatgcca aagganatat acatttcaat totocaaact tottoctcat tocaagagtt
                                                                        180
ttcaatattt gcatgaacct gctgataanc catgttaana aacaaatatc tctctnacct
                                                                        240
tctcatcggt
                                                                        250
      <210> 214
      <211> 444
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (444)
      <223> n = A, T, C or G
      <400> 214
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gatttaatgt tgtctcagct tgggcacttc agttaggacc taaggatgcc agccggcagg
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tttatatatg cagcaacaat attcaagcgc gacaacaggt tattgaactt gcccgccagt
                                                                        180
tgaatttcat tcccattgac ttgggatcct tatcatcagc canagagatt gaaaatttac
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ccctacgact ctttactctc tggagagggc cagtggtggt agctataagc ttggccacat
                                                                        300
tttttttcc tttattcctt tgtcagagat gcgattcatc catatgctan aaaccaacag
                                                                        360
agtgactttt acaaaattcc tataganatt gtgaataaaa ccttacctat agttgccatt
                                                                        420
actttgctct ccctaatata cctc
                                                                        444
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      <211> 366
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      <221> misc_feature
      <222> (1) ... (366)
      <223> n = A, T, C or G
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                                                                       120
cattatgcca aagganatat acatttcaat tctccaaact tcttcctcat tccaagagtt
                                                                       180
ttcaatattt gcatgaacct gctgataagc catgttgaga aacaaatatc tctctgacct
                                                                       240
tctcatcggt aagcagaggc tgtaggcaac atggaccata gcgaanaaaa aacttagtaa
                                                                       300
tecaagetgt tttetacaet gtaaceaggt ttecaaceaa ggtggaaate teetataett
                                                                       360
ggtgcc
                                                                       366
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       <212> DNA
       <213> Homo sapien
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       <222> (1) ... (260)
       <223> n = A, T, C or G
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caagacaggg gcctaaggag ggtctccaca ctgctnntaa gggctnttnc attttttat
                                                                           120
taataaaaag tnnaaaaggc ctcttctcaa cttttttccc ttnggctgga aaatttaaaa
                                                                           180
atcaaaaatt tootnaagtt ntoaagctat catatatact ntatootgaa aaagcaacat
                                                                           240
aattottoot toootoottt
                                                                           260
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       <211> 262
       <212> DNA
       <213> Homo sapien
      <220>
      <221> misc_feature
      \langle 222 \rangle (1)...(262)
\langle 223 \rangle n = A,T,C or G
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                                                                            60
tcttgcctat aattttctat tttaataagg aaatagcaaa ttggggtggg gggaatgtag
                                                                          120
ggcattctac agtttgagca aaatgcaatt aaatgtggaa ggacagcact gaaaaatttt
                                                                           180
atgaataato tgtatgatta tatgtotota gagtagattt ataattagoo acttacoota
                                                                           240
atatccttca tgcttgtaaa gt
                                                                          262
      <210> 218
<211> 205
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
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      <223> n = A, T, C or G
      <400> 218
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cccctatcaa ctcccttttg tagtaaactt ggaaccttgg aaatgaccag gccaagactc
                                                                          120
aggcetecce agttetactg acetttgtee ttangtntna ngtecagggt tgetaggaaa
                                                                          180
anaaatcagc agacacaggt gtaaa
                                                                          205
      <210> 219
      <211> 114
      <212> DNA
      <213> Homo sapien
      <400> 219
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                                                                           60
accacgaagt tgatttctct tgtgtgcaga gtgactgatt ttaaaggaca tgga
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      <211> 93
      <212> DNA
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<213> Homo sapien <400> 220 actagecage acaaaaggea gggtageetg aattgettte tgetetttae atttetttta 60 93 aaataagcat ttagtgctca gtccctactg agt <210> 221 <211> 167 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1)...(167) <223> n = A, T, C or G<400> 221 actanqtqca qqtqcqcaca aatatttqtc qatattccct tcatcttqqa ttccatqaqq 60 120 tettttgece ageetgtgge tetactgtag taagtttetg etgatgagga geeagnatge ccccactac cttccctgac gctccccana aatcacccaa cctctgt . 167 <210> 222 <211> 351 <212> DNA <213> Homo sapien <400> 222 agggcgtggt gcggagggcg gtactgacct cattagtagg aggatgcatt ctggcacccc 60 120 gttcttcacc tgtcccccaa tccttaaaag gccatactgc ataaagtcaa caacagataa 180 atgtttgctq aattaaagga tggatqaaaa aaattaataa tgaatttttg cataatccaa ttttctcttt tatatttcta gaagaagttt ctttgagcct attagatccc gggaatcttt 240 taggtgagca tgattagaga gcttgtaggt tgcttttaca tatatctggc atatttgagt 300 ctcgtatcaa aacaatagat tggtaaaggt ggtattattg tattgataag t 351 <210> 223 <211> 383 <212> DNA <213> Homo sapien <220> <221> misc feature <222> (1) ... (383) <223> n = A, T, C or G<400> 223 60 aaaacaaaca aacaaaaaa acaattcttc attcagaaaa attatcttag ggactgatat tggtaattat ggtcaattta atwrtrttkt ggggcatttc cttacattgt cttgacaaga 120 ttaaaatgtc tgtgccaaaa ttttgtattt tatttggaga cttcttatca aaagtaatgc 180 tqccaaaqqa aqtctaaqqa attagtagtq ttcccmtcac ttgtttggag tgtgctattc 240 taaaagattt tgatttoctg gaatgacaat tatattttaa ctttggtggg ggaaanagtt 300 ataggaccac agtetteact tetgataett gtaaattaat ettttattge aettgttttg 360 accattaagc tatatgttta aaa 383 <210> 224 <211> 320 <212> DNA <213> Homo sapien <400> 224 cccctgaagg cttcttgtta gaaaatagta cagttacaac caataggaac aacaaaaaga 60 aaaagtttgt gacattgtag tagggagtgt gtacccctta ctccccatca aaaaaaaaat 120 ggatacatgg ttaaaggata raagggcaat attttatcat atgttctaaa agagaaggaa 180

gagaaaatac tactttete aaatgtggcc gtccatecte tttaractem gcattgtgad	c ctttaragtt	ccttaaaggt gcatgacttg	gctttgatac gacacggtaa	tgaaggacac ctgttgcagt	240 300 320
<210> 225 <211> 1214 <212> DNA <213> Homo sapi	Len		•		
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<pre>&lt;210&gt; 226 &lt;211&gt; 119 &lt;212&gt; DNA &lt;213&gt; Homo sapio</pre>	en			·	1214
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<213> Homo sapien

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tegtggeega eetggeetet eetggeetgt ttettaagat geggagteae attteaatgg
                                                                       180
taggaaaagt ggcttcgtaa aatagaagag cagtcactgt ggaactacca aatggcgaga
                                                                       240
                                                                       300
tqctcqqtqc acattqqqqt gctttqqqat aaaagattta tgagccaact attctctggc
accagattct aggccagttt gttccactga agcttttccc acagcagtcc acctctgcag
                                                                       360
                                                                       420
gctggcagct gaatggcttg ccggtggctc tgtggcaaga tcacactgag atcgatgggt
gagaaggcta ggatgcttgt ctagtgttct tagctgtcac gttggctcct tccaggttgg
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ccagacggtg ttggccactc ccttctaaaa cacaggcgcc ctcctggtga cagtgacccg
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ccqtqqtatq ccttqqccca ttccaqcaqt cccaqttatg catttcaagt ttggggtttg
                                                                       600
                                                                       660
ttcttttcqt taatqttcct ctqtgttgtc aqctqtcttc atttcctggg ctaagcagca
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ttgggagatg tggaccagag atccactcct taagaaccag tggcgaaaga cactttcttt
cttcactctg aagtagctgg tggt
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                                                                       120
cattacacat cqaaataaaa gaaaqqtqgc agacttgccc aacgccaggc tgacatgtgc
tgcagggttg ttgtttttta attattattg ttagaaacgt cacccacagt ccctgttaat
                                                                       180
ttgtatgtga cagccaactc tgagaaggtc ctatttttcc acctgcagag gatccagtct
                                                                       240
                                                                       300
cactaggete etcettgece teacactgga gteteegeea gtgtgggtge ecactgaeat
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gagcgacagt tcaaggagga gaagcttgca gagcagctca agcaagctga ggagctcagg
                                                                       120
                                                                       180
caatataaag tootggttoa cactoaggaa cgagagotga cocagttaag ggagaagttg
cgggaaggga gagatgcctc cctctcattg aatgagcatc tccaggccct cctcactccg
                                                                       240
gatgaaccgg acaagtccca ggggcaggac ctccaagaaa cagacctcgg ccgcgaccac
                                                                       300
                                                                       301
      <210> 231
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 231
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caggaactcc aagtccacat ccttggcaac tggggacttg cgcaggttag ccttgaggat
ggcaacacgg gacttctcat caggaagtgg gatgtagatg agctgatcaa gacggccagg
                                                                       180
                                                                       240
tctqaqqatq qcaqqatcaa tqatqtcagg ccggttggta ccgccaatga tgaacacatt
                                                                       300
ttttttttgtg gacatgccat ccatttctgt caggatctgg ttgatgactc ggtcagcagc
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 cgtgctgtac caagtgctgg tgccagcctg ttacctgttc tcactgaaaa tctggctaat
                                                                        240
 getettgtgt atcacttetg attetgacaa teaateaate aatggeetag ageaetgaet
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                                                                        301
       <210> 233
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 233
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atgctaaggc cccagagatc gtttgatcca accetettat tttcagaggg gaaaatgggg
                                                                        120
cctagaagtt acagagcatc tagctggtgc gctggcaccc ctggcctcac acagactccc
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gagtagctgg gactacaggc acacagtcac tgaagcaggc cctgttagca attctatgcq
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tacaaattaa catgagatga gtagagactt tattgagaaa gcaaqagaaa atcctatcaa
                                                                        300
                                                                        301
       <210> 234
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                                                                        120
tcaatttcag caacatactt ctcaatttct tcaggattta aaatcttgag ggattgatct
                                                                        180
cgcctcatga cagcaagttc aatgtttttg ccacctgact gaaccacttc caggagtgcc
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ttgatcacca gcttaatggt cagatcatct gcttcaatgg cttcgtcagt atagttcttc
                                                                        300
                                                                        301
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      <211> 283
      <212> DNA
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aattccctca tcttttaggg aatcatttac caggtttgga gaggattcag acagctcagg
                                                                        120
tgctttcact aatgtctctg aacttctgtc cctctttgtt catggatagt ccaataaata
                                                                       180
atgttatett tgaactgatg etcataggag agaatataag aactetgagt gatateaaca
                                                                        240
ttagggattc aaagaaatat tagatttaag ctcacactgg tca
                                                                        283
      <210> 236
      <211> 301
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aatactttta aatcgatcag atttccctaa cccacatgca atcttcttca ccagaagagg
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tcggagcagc atcattaata ccaagcagaa tgcgtaatag ataaatacaa tggtatatag
                                                                       180
tgggtagacg gcttcatgag tacagtgtac tgtggtatcg taatctggac ttgggttgta
                                                                       240
aagcatcgtg taccagtcag aaagcatcaa tactcgacat gaacgaatat aaagaacacc
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<212> DNA <213> Homo sapien <400> 242 ccgaggtcct gggatgcaac caatcactct gtttcacgtg acttttatca ccatacaatt 60 tgtggcattt cctcattttc tacattgtag aatcaagagt gtaaataaat gtatatcgat 120 gicitcaaga atatatcatt cottiticac tagaacccat icaaaatata agicaaqaat 180 cttaatatca acaaatatat caagcaaact ggaaggcaga ataactacca taatttaqta 240 taagtaccca aagttttata aatcaaaagc cctaatgata accattttta gaattcaatc 300 301 <210> 243 <211> 301 <212> DNA <213> Homo sapien <400> 243 aggtaagtcc cagtttgaag ctcaaaagat ctggtatgag cataggctca tcgacgacat 60 ggtggcccaa gctatgaaat cagagggagg cttcatctgg gcctgtaaaa actatgatgg 120 tgacgtgcag tcggactctg tggcccaagg gtatggctct ctcgqcatga tgaccaqcgt 180 gctggtttgt ccagatggca agacagtaga agcagaggct gcccacggga ctgtaacccg 240 teactacege atgttecaga aaggacagga gaegtecace aateceattg ettecatttt 300 301 <210> 244 <211> 300 <212> DNA <213> Homo sapien gctggtttgc aagaatgaaa tgaatgattc tacaqctagg acttaacctt gaaatggaaa 60 gtcatgcaat cccatttgca ggatctgtct gtgcacatgc ctctgtagag agcagcattc 120 ccagggacct tggaaacagt tgacactgta aggtgcttgc tccccaagac acatcctaaa 180 aggtgttgta atggtgaaaa cgtcttcctt ctttattgcc ccttcttatt tatgtgaaca 240 actgtttgtc ttttgtgtat cttttttaaa ctgtaaagtt caattgtgaa aatgaatatc 300 <210> 245 <211> 301 <212> DNA <213> Homo sapien <400> 245 gtctgagtat ttaaaatgtt attgaaatta tccccaacca atgttagaaa agaaagaggt 60 tatatactta gataaaaaat gaggtgaatt actatccatt gaaatcatgc tcttagaatt 120 aaggccagga gatattgtca ttaatgtara cttcaggaca ctagagtata gcagccctat 180 gttttcaaag agcagagatg caattaaata ttgtttagca tcaaaaaggc cactcaatac 240 agctaataaa atgaaagacc taatttctaa agcaattctt tataatttac aaagttttaa 300 301 <210> 246 <211> 301 <212> DNA <213> Homo sapien <400> 246 qqtctqtcct acaatqcctq cttcttqaaa qaaqtcqqca ctttctaqaa taqctaaata 60 acctgggctt attttaaaga actatttgta gctcagattg gttttcctat ggctaaaata 120 agtgcttctt gtgaaaatta aataaaacag ttaattcaaa gccttgatat atgttaccac 180 taacaatcat actaaatata ttttgaagta caaagtttga catgctctaa agtgacaacc 240 caaatgtgtc ttacaaaaca cgttcctaac aaggtatgct ttacactacc aatgcagaaa 300 С 301

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       <212> DNA
       <213> Homo sapien
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                                                                          120
gtgtcctgtg ttcaggtgcg acacacaatc ctcatgggaa caggatcacc catgcgctgc
                                                                          180
ccttgatgat caaggttggg gcttaagtgg attaagggag gcaagttctg qqttccttqc
                                                                          240
cttttcaaac catgaagtca ggctctgtat ccctcctttt cctaactgat attctaacta
                                                                          300
                                                                          301
      <210> 248
       <211> 301
       <212> DNA
      <213> Homo sapien
      <400> 248
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attaggaaga ttcttagggg taatttttct gaggaaggag aactagccaa cttaagaatt
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acaggaagaa agtggtttgg aagacagcca aagaaataaa agcagattaa attgtatcag
                                                                          180
gtacattcca gcctgttggc aactccataa aaacatttca gattttaatc ccgaatttag
                                                                          240
ctaatgagac tggatttttg ttttttatgt tgtgtgtcgc agagctaaaa actcagttcc
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                                                                          301
      <210> 249
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 249
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coctgacqct gctgttctcc ccgaaaaacc cgaccgacct ccgcgatctc cgtcccgccc
                                                                          120
ccagggagac acagcagtga ctcagagctg gtcgcacact gtgcctccct cctcaccgcc
                                                                          180
catcgtaatg aattattttg aaaattaatt ccaccatcct ttcagattct ggatggaaag
                                                                          240
actgaatctt tgactcagaa ttgtttgctg aaaagaatga tgtgactttc ttaqtcattt
                                                                          300
                                                                          301
      <210> 250
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 250
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cttatcttta ttggcttgat aaacataatt atttctaaca ctagcttatt tccagttgcc
                                                                          120
cataagcaca tcagtacttt tctctggctg gaatagtaaa ctaaagtatg gtacatctac ctaaaagact actatgtgga ataatacata ctaatgaagt attacatgat ttaaagacta
                                                                          180
                                                                          240
caataaaacc aaacatgctt ataacattaa gaaaaacaat aaagatacat gattgaaacc
                                                                          300
                                                                          301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 251
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agacaacctc atagagcata ggagaactgg ttgccctggg ggcagqqqqa ctqtctqqat
                                                                          120
qqcaqqqqtc ctcaaaaatq ccactqtcac tqccaqqaaa tqcttctqaq caqtacacct
                                                                          180
cattgggatc aatgaaaagc ttcaagaaat cttcaggctc actctcttga aggcccggaa
                                                                          240
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cctctggagg ggggcagtgg c	aatcccagct	: ccaggacgga	tcctgtcgaa	aagatatcct	300 301
<210> 252 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 253 <211> 301 <212> DNA <213> Homo sapid	en				
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<210> 254 <211> 301 <212> DNA <213> Homo sapie	en				
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<210> 255 <211> 302 <212> DNA <213> Homo sapie	∙n				
· <400> 255 agcttttttt ttttttttt attactgaaa tgtttctttt tgggattttg ttgagttctt aggaaaaagg actggaggtg aacattatta aaaaacaaga aa	ctgaatataa caagcatctc gaatctttat	atataaatat ctaataccct aaaaaacaag	gtgcaaagtt caagggcctg agtgattgag	tgacttggat agtagggggg gcagattgta	60 120 180 240 300 302
<210> 256 <211> 301 <212> DNA <213> Homo sapie	n				
<220> <221> misc_featu	re				

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                                                                        120
acceccaaaa geetggacae ettgageaca eagttatgae eaggacagae teatetetat
                                                                        180
aggcaaatag ctgctggcaa actggcatta cctggtttgt ggggatgggg gggcaagtgt
                                                                        240
                                                                        300
qtqqcctctc qqcctqqtta gcaagaacat tcagggtagg cctaagttan tcgtgttagt
                                                                        301
      <210> 257
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 257
gttgtggagg aactctggct tgctcattaa gtcctactga ttttcactat cccctgaatt
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tecceactta tttttgtett teactatege aggeettaga agaggtetae etgeeteeag
                                                                        120
                                                                        180
tottacctaq tocaqtotac cocctggagt tagaatggcc atoctgaagt gaaaagtaat
gtcacattac tecetteagt gatttettgt agaagtgeea atecetgaat gecaceaaga
                                                                        240
tottaatott cacatottta atottatoto titgactoot otttacacog gagaaggoto
                                                                        300
                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
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aggggcccag ccaccaggcg cagaagcaag ataaacagta ggctcaagac cagagccacc
                                                                        120
cccagggcaa caagaatcca ataccaggac tgggcaaaat cttcaaagat cttaacactg
                                                                        180
                                                                        240
atqtctcqqq cattqaqqct gtcaataana cgctgatccc ctgctgtatg gtggtgtcat
                                                                        300
tqqtqatccc tqqqaqcqcc qqtgqagtaa cgttggtcca tggaaagcag cgcccacaac
                                                                        301
t
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      <211> 301
      <212> DNA
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      <221> misc_feature
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      <223> n = A, T, C or G
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qtqtcctqaa qtqatttqqa cccctqaqqq cagacaccta agtaggaatc ccagtgggaa
gcaaagccat aaggaagccc aggattcctt gtgatcagga agtgggccag gaaggtctgt
                                                                        180
tocageteae ateteatety catgeageae ggaceggaty egeceaetgg gtettggett
                                                                        240
                                                                        300
coctcocate tteteaagea gtgteettgt tgagecattt geateettgg eteeaggtgg
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      <210> 260
      <211> 301
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<212> DNA
       <213> Homo sapien
       <400> 260
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 aaggtgtctt aacttgaaaa agattaggag tcactggttt acaagttata attgaatgaa
                                                                        120
 agaactgtaa cagccacagt tggccatttc atgccaatgg cagcaaacaa caggattaac
                                                                        180
 tagggcaaaa taaataagtg tgtggaagcc ctgataagtg cttaataaac agactgattc
                                                                         240
 actgagacat cagtacctgc ccgggcggcc gctcgagccg aattctgcag atatccatca
                                                                        300
                                                                        301
       <210> 261
       <211> 301
       <212> DNA
       <213> Homo sapien
       <400> 261
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totgottoca tocacgatto tagoaatgac ototoggaca toaaagotoo tottaaggtt
                                                                        120
agcaccaact attocataca attoatcago aggaaataaa ggotottoag aaggttoaat
                                                                        180
ggtgacatcc aatttcttct gataatttag attcctcaca accttcctag ttaagtgaag
                                                                        240
ggcatgatga tcatccaaag cccagtggtc acttactcca gactttctgc aatgaagatc
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                                                                        301
      <210> 262
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 262
gaggagagcc tgttacagca tttgtaagca cagaatactc caggagtatt tgtaattgtc
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tgtgagette ttgccgcaag tetetcagaa atttaaaaag atgcaaatce etgagtcace
                                                                        120
cctagacttc ctaaaccaga tcctctgggg ctggaacctg gcactctgca tttgtaatga
                                                                        180
gggetttetg gtgeacacct aattttgtge atctttgeec taaatcctgg attagtgeec
                                                                        240
catcattacc cccacattat aatgggatag attcagagca gatactctcc agcaaagaat
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                                                                        301
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aaaattacta ottaatoota attoacaata acaatggoat taaggtttga ottgagttgg
                                                                       120
ttcttagtat tatttatggt aaataggctc ttaccacttg caaataactg gccacatcat
                                                                       180
taatgactga cttcccagta aggctctcta aggggtaagt angaggatcc acaggatttg
                                                                       240
agatgctaag gccccagaga tcgtttgatc caaccctctt attttcagag gggaaaatgg
                                                                       300
                                                                       301
      <210> 264
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 264
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aatgaatgac totaaaaaca atattacat ttaatggttt gtagacaata aaaaaacaag gtggatagat otagaattgt aacattttaa gaaaaccata scatttgaca gatgagaaag otcaattata gatgcaaagt tataactaaa otactatagt agtaaagaaa tacatttcac accottcata taaattcact atottggott gaggcactoc ataaaatgta toacgtgcat a	120 180 240 300 301
<210> 265 <211> 301 <212> DNA <213> Homo sapien	
<pre>&lt;400&gt; 265 tgcccaagtt atgtgtaagt gtatccgcac ccagaggtaa aactacactg tcatctttgt cttcttgtga cgcagtattt cttctctggg gagaagccgg gaagtcttct cctggctcta catattcttg gaagtctcta atcaactttt gttccatttg tttcatttct tcaggaggga ttttcagttt gtcaacatgt tctctaacaa cacttgccca tttctgtaaa gaatccaaag cagtccaagg ctttgacatg tcaacaacca gcataactag agtatccttc agagatacgg c</pre>	60 120 180 240 300 301
<210> 266 <211> 301 <212> DNA <213> Homo sapien	
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<210> 267 <211> 301 <212> DNA <213> Homo sapien	
<400> 267 aaagagcaca ggccagctca gcctgccctg gccatctaga ctcagcctgg ctccatgggg gttctcagtg ctgagtccat ccaggaaaag ctcacctaga ccttctgagg ctgaatcttc atcctcacag gcagcttctg agagcctgat attcctagcc ttgatggtct ggagtaaagc ctcattctga ttcctctcct tcttttcttt	60 120 180 240 300 301
<210> 268 <211> 301 <212> DNA <213> Homo sapien	
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<210> 269 <211> 301 <212> DNA <213> Homo sapien	

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                                                                       120
atagtcacag accttaaata ttcacattgt tttctatgtc tactgaaaat aagttcacta
                                                                       180
cttttctgga tattctttac aaaatcttat taaaattcct ggtattatca cccccaatta
                                                                       240
tacagtagca caaccacctt atgtagtttt tacatgatag ctctgtagaa gtttcacatc
                                                                       300
                                                                       301
      <210> 270
     <211> 301
      <212> DNA
     <213> Homo sapien
     <400> 270
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                                                                        60.
                                                                       120
cacaagaata catatteett ttatttetaa ggagttaaac atagatgtag etgatgtgga
gagettgetg gtgeagtgea tattggataa cactatteat ggeegaattg ateaagteaa
                                                                       180
                                                                       240
ccaactcctt gaactggatc atcagaagaa gggtggtgca cgatatactg cactagataa
                                                                       300
tgqaccaacc aactaaattc tctcaccagg ctgtatcagt aaactggctt aacagaaaac
                                                                       301
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      <211> 301
      <212> DNA
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     <221> misc_feature
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     <223> n = A,T,C or G
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tttatagete atetttaggg ttgatattea gtteatgett ecettgetgt tettgateea
                                                                       120
                                                                       180
quattycaat cacttcatca gcctgtattc gctccaattc tctataaagt gggtccaagg
tgaaccacag agccacagca cacctctttc ccttggtgac tgccttcacc ccatganggt
                                                                       240
                                                                       300
tototoctoc agatganaac tgatcatgog cocacatttt gggttttata gaagcagtca
      <210> 272
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 272
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ttatcagaaa accaaatgag cctggaatct tcataatacc taaacatgcc gtatttagga
                                                                       120
                                                                       180
tocaataatt coctoatgat gagcaagaaa aattotttgc gcacccotcc tgcatccaca
gcatcttctc caacaaatat aaccttgagt ggcttcttgt aatctatgtt ctttgttttc
                                                                       240
ctaaggactt ccattgcatc tcctacaata tittctctac gcaccactag aattaagcag
                                                                       300
                                                                       301
      <210> 273
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(301)
      <223> n = A, T, C or G
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<213> Homo sapien

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 agagangetg ggacatggat aatcacwtaa tttgctayta tyactttaat ctgactygaa
                                                                        120
 gaaccgtcta aaaataaaat ttaccatgtc dtatattcct tatagtatgc ttatttcacc
                                                                        180
 ttytttetgt ccagagagag tatcagtgac ananatttma gggtgaamac atgmattggt
                                                                        240
 gggacttnty tttacngagm accetgeecg sgegeecteg makengantt eegesanane
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                                                                        301
       <210> 274
       <211> 301
       <212> DNA
       <213> Homo sapien
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       <221> misc_feature
       <222> (1)...(301)
       <223> n = A, T, C or G
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aacagtaaat gattattaga gagaangaat ggaccaagga gacagaaatt aacttgtaaa
                                                                        120
tgattctctt tggaatctga atgagatcaa gaggccagct ttagcttgtg gaaaagtcca
                                                                        180
totaggtatg gttgcattct cgtcttcttt tctgcagtag ataatgaggt aaccgaaggc
                                                                        240
aattgtgctt cttttgataa gaagctttct tggtcatatc aggaaattcc aganaaagtc
                                                                        300
С
                                                                        301
      <210> 275
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc_feature
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      <223> n = A, T, C or G
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gggtgaaatt ggccaacttt ctattaactt atgttggcaa ttttgccacc aacagtaagc
                                                                        120
tggcccttct aataaaagaa aattgaaagg tttctcacta aacggaatta agtagtggag
                                                                       180
tcaagagact cccaggcctc agcgtacctg cccgggcggc cgctcgaagc cgaattctgc
                                                                        240
agatatccat cacactggcg gncgctcgan catgcatcta gaaggnccaa ttcgccctat
                                                                        300
      <210> 276
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 276
tgtacacata ctcaataaat aaatgactgc attgtggtat tattactata ctgattatat
ttatcatgtg acttctaatt agaaaatgta tccaaaagca aaacagcaga tatacaaaat
                                                                       120
taaagagaca gaagatagac attaacagat aaggcaactt atacattgag aatccaaatc
                                                                       180
caatacattt aaacatttgg gaaatgaggg ggacaaatgg aagccagatc aaatttgtgt
                                                                       240
aaaactattc agtatgtttc ccttgcttca tgtctgagaa ggctctcctt caatggggat
                                                                       300
                                                                       301
     <210> 277
     <211> 301
     <212> DNA
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<220>
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       <222> (1)...(301)
       <223> n = A, T, C or G
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                                                                          60
 atacagagga cttggaggaa gcagagcaac tgaatttaat ttaaaagaag gaaaacattg
                                                                         120
 qaatcatqqc actcctgata ctttcccaaa tcaacactct caatgcccca ccctcgtcct
                                                                         180
 caccatagtg gggagactaa agtggccacg gatttgcctt angtgtgcag tgcgttctga
                                                                         240
 gttenetgte gattacatet gaccagtete ettttteega agteenteeg ticaatetig
                                                                         300
                                                                         301
       <210> 278
       <211> 301
       <212> DNA
       <213> Homo sapien
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       <223> n = A, T, C or G
       <400> 278
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                                                                          60
 aacatatcaa atgaaacagg gaaaatgaag ctgacaattt atggaagcca gggcttgtca
                                                                         120
 cagtetetae tgttattatg cattacetgg gaatttatat aageeettaa taataatgee
                                                                         180
 aatqaacatc tcatqtqtqc tcacaatqtt ctqqcactat tataaqtqct tcacaqqttt
                                                                         240
tatgtgttet tegtaacttt atggantagg taeteggeeg egaacaeget aageegaatt
                                                                         300
                                                                         301
       <210> 279
       <211> 301
       <212> DNA
       <213> Homo sapien
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       <221> misc_feature
       <222> (1) ... (301)
       <223> n = A, T, C or G
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 qttatattaa ttgccaatat aagtaaatat agattatata tgtatagtgt ttcacaaagc
                                                                         120
 ttagaccttt accttccagc caccccacag tgcttgatat ttcagagtca gtcattggtt
                                                                         180
                                                                         240
 atacatgtgt agttccaaag cacataagct agaanaanaa atatttctag ggagcactac
 catctgtttt cacatgaaat gccacacaca tagaactcca acatcaattt cattgcacag
                                                                         300
                                                                         301
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       <211> 301
       <212> DNA
    . <213> Homo sapien
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ggtactggag ttttcctccc ctgtgaaaac gtaactactg ttgggagtga attgaggatg
                                                                          60
                                                                         120
 tagaaaggtg gtggaaccaa attgtggtca atggaaatag gagaatatgg ttctcactct
 tgagaaaaaa acctaagatt agcccaggta gttgcctgta acttcagttt ttctgcctgg
                                                                         180
gtttgatata gtttagggtt ggggttagat taagatctaa attacatcag gacaaagaga
                                                                         240
cagactatta actocacagt taattaagga ggtatgttoc atgtttattt gttaaagcag
                                                                         300
                                                                         301
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<210> 281
      <211> 301
      <212> DNA
      <213> Homo sapien
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gccgagcaat ccaaatcctg aatgaagggg catcttctga aaaaggagat ctgaatctca
                                                                        120
atgtggtagc aatggcttta tcgggttata cggatgagaa gaactccctt tggagagaaa
                                                                        180
tgtgtagcac actgcgatta cagctaaata acccgtattt gtgtgtcatg tttgcatttc
                                                                        240
tgacaagtga aacaggatct tacgatggag ttttgtatga aaacaaagtt gcagtacctc
                                                                        300
                                                                        301
      <210> 282
      <211> 301
      <212> DNA
      <213> Homo sapien
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tocagaacco aaaaattaag aaattcaaaa agacattttg tgggcacctg ctagcacaga
                                                                        120
agcgcagaag caaagcccag gcagaaccat gctaacctta cagctcagcc tgcacagaag
                                                                        180
cgcagaagca aagcccaggc agaaccatgc taaccttaca gctcagcctg cacagaagcg
                                                                        240
cagaagcaaa gcccaggcag aacatgctaa ccttacagct cagcctgcac agaagcacag
                                                                        300
                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
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                                                                         60
cactttgagg gctttataat aatatgctgc ttgaaaaaaa aaatgtgtag ttgatactca
                                                                        120
gtgcatctcc agacatagta aggggttgct ctgaccaatc aggtgatcat tttttctatc
                                                                        180
acttcccagg ttttatgcaa aaattttgtt aaattctata atggtgatat gcatctttta
                                                                       240
ggaaacatat acatttttaa aaatctattt tatgtaagaa ctgacagacg aatttqcttt
                                                                        300
                                                                       301
      <210> 284
      <211> 301
      <212> DNA
      <213> Homo sapien
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gettegtgtg tgggcaaage aacatettee etaaatatat attaccaaga aaageaagaa
                                                                       120
gcagattagg tttttgacaa aacaaacagg ccaaaagggg gctgacctgg agcagagcat
                                                                       180
ggtgagaggc aaggcatgag agggcaagtt tgttgtggac agatctgtgc ctactttatt
                                                                       240
actggagtaa aagaaaacaa agttcattga tgtcgaagga tatatacagt gttagaaatt
                                                                       300
                                                                       301
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      <211> 301
      <212> DNA
     <213> Homo sapien
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     <221> misc_feature
     <222> (1)...(301)
     <223> n = A, T, C or G
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<210> 286 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 287 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 288 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 289 <211> 301 <212> DNA <213> Homo sapi	en				
<220> <221> misc_feat <222> (1)(30 <223> n = A,T,C	1)				
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cgttctataa atgaatgtgc tgaagcaaag tgcccatggt ggcggcgaan aagagaaaga
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 tgtgttttgt tttggactet etgtggtece ttecaatget gtgggtttee aaccagngga
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                                                                        301
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       <211> 301
       <212> DNA
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       <222> (1) ... (301)
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                                                                        120
ttctgacctc cttttctaat cacagtaggg atagaggcag anccacctac aatgaacatg
                                                                        180
gagttctatc aagaggcaga aacagcacag aatcccagtt ttaccattcg ctagcagtgc
                                                                        240
tgccttgaac aaaaacattt ctccatgtct cattttcttc atgcctcaag taacagtgag
                                                                        300
                                                                        301
      <210> 291
      <211> 301
      <212> DNA
      <213> Homo sapien
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                                                                         60
tatatcaget agatttttt tetatgettt acetgetatg gaaaatttga cacattetge
                                                                        120
tttactcttt tgtttatagg tgaatcacaa aatgtatttt tatgtattct gtagttcaat
                                                                        180
agccatggct gtttacttca tttaatttat ttagcataaa gacattatga aaaggcctaa
                                                                        240
acatgagett cactteecca etaactaatt ageatetgtt atttettaac egtaatgeet
                                                                        300
                                                                        301
      <210> 292
      <211> 301
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (301)
      <223> n = A,T,C or G
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tgtattaaat aatttttaag tttaaaagat aaaataccat cattttaaat gttggtattc
                                                                       120
aaaaccaaag natataaccg aaaggaaaaa cagatgagac ataaaatgat ttgcnagatg
                                                                       180
ggaaatatag tasttyatga atgttnatta aattccagtt ataatagtgg ctacacactc
                                                                       240
teactacaca cacagaeeee acagteetat atgecacaaa cacattteca taacttgaaa
                                                                       300
а
                                                                       301
      <210> 293
      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 293
ggtaccaagt gctggtgcca gcctgttacc tgttctcact gaaaagtctg gctaatgctc
                                                                        60
ttgtgtagtc acttctgatt ctgacaatca atcaatcaat ggcctagagc actgactgtt
                                                                       120
aacacaaacg tcactagcaa agtagcaaca gctttaagtc taaatacaaa gctgttctgt
                                                                       180
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gtgagaattt tttaaaaggo ccgcgaccac gctaagccga g	_			, ,,	240 300 301
<210> 294 <211> 301 <212> DNA <213> Homo sapi	en <sub>.</sub>				
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<210> 295 <211> 305 <212> DNA <213> Homo sapi	en				
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<210> 296 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 297 <211> 300 <212> DNA ** <213> Homo sapi	en '				
<220> <221> misc_feat <222> (1)(30 <223> n = A,T,C	0)				
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tocatcattg ggagtgcact accgcacctc ggccgcgacc					240 300
<210> 298 <211> 301 <212> DNA <213> Homo sapi	en				
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<210> 299 <211> 301 <212> DNA <213> Homo sapid	en				
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<210> 300 <211> 301 <212> DNA <213> Homo sapie	en				
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<210> 301 <211> 301 <212> DNA <213> Homo sapie	en.				
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<210> 302 <211> 301					

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<212> DNA
      <213> Homo sapien
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tgaattttga aaattactac ttaatcctaa ttcacaataa caatggcatt aaggtttgac
                                                                        120
                                                                        180
tigagttggt tettagtatt atttatggta aataggetet taccaettge aaataactgg
ccacatcatt aatqactqac ttcccagtaa ggctctctaa ggggtaagta ggaggatcca
                                                                        240
caggatttga gatgctaagg ccccagagat cgtttgatcc aaccctctta ttttcagagg
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                                                                        301
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      <211> 301
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      <400> 303
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                                                                        120
                                                                        180
tggctaatgg aactaccgct tgcatgttaa aaatggtggt ttgtgaaatg atcataggcc
agtaacgggt atgttttct aactgatctt ttgctcgttc caaagggacc tcaagacttc
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catcgatttt atatctgggg tctagaaaag gagttaatct gttttccctc ataaattcac
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                                                                        301
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      <211> 301
      <212> DNA
      <213> Homo sapien
      <400> 304
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tattagtttc agtttcagct tacccacttt ttgtctgcaa catgcaraas agacagtgcc
                                                                        120
ctttttagtg tatcatatca ggaatcatct cacattggtt tgtgccatta ctggtgcagt
                                                                        180
                                                                        240
qactttcaqc cacttgggta aggtggagtt ggccatatgt ctccactgca aaattactga
                                                                        300
ttttcctttt gtaattaata agtgtgtgtg tgaagattct ttgagatgag gtatatatct
                                                                        301
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    · <211> 301
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      <221> misc_feature
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      <223> n = A, T, C \text{ or } G
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caqqqqaca gacctggaca gacacgttgt catttgctgc tgtgggtagg aaaatgggcg
taaaggagga gaaacagata caaaatctcc aactcagtat taaggtattc tcatgcctag
                                                                        180
aatattggta gaaacaagaa tacattcata tggcaaataa ctaaccatgg tggaacaaaa
                                                                        240
                                                                        300
ttctqqqatt taaqttqqat accaangaaa ttgtattaaa agagctgttc atggaataag
                                                                        3Q1
      <210> 306
      <211> 8
      <212> PRT
      <213> Homo sapien
      <400> 306
Val Leu Gly Trp Val Ala Glu Leu
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. . . . .

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1
                  5
       <210> 307
       <211> 637
       <212> DNA
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 attgaggaat gatacttgag cccaaagagc attcaatcat tgttttattt gccttmtttt
                                                                        180
 cacaccattg gtgagggagg gattaccacc ctggggttat gaagatggtt gaacacccca
                                                                        240
cacatagcac eggagatatg agateaacag tttettagee atagagatte acageecaga
                                                                        300
 qcaggaggac gcttgcacac catgcaggat gacatggggg atgcgctcgg gattggtgt
                                                                        360
aagaagcaag gactgttaga ggcaggcttt atagtaacaa gacggtgggg caaactctga
                                                                        420
tttccgtggg ggaatgtcat ggtcttgctt tactaagttt tgagactggc aggtagtgaa
                                                                        480
actcattagg ctgagaacct tgtggaatgc acttgaccca sctgatagag gaagtagcca
                                                                        540
ggtgggagcc tttcccagtg ggtgtgggac atatctggca agattttgtg gcactcctgg
                                                                        600
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                                                                        637
      <210> 308
      <211> 647
      <212> DNA
      <213> Homo sapien
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      <221> misc feature
      <222> (1) ... (647)
      \langle 223 \rangle n = A, T, C or G
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                                                                        120
ggngcctcac agtatagatc tggtagcaaa gaagaagaaa caaacactga tctctttctg
                                                                        180
ccacccctct gaccctttgg aactcctctg accctttaga acaagcctac ctaatatctg
                                                                        240
ctagagaaaa gaccaacaac ggcctcaaag gatctcttac catgaaggtc tcagctaatt
                                                                        300
cttggctaag atgtgggttc cacattaggt tctgaatatg gggggaaggg tcaatttgct
                                                                        360
cattltgtgt gtggataaag tcaggatgcc caggggccag agcagggggc tgcttgcttt
                                                                        420
gggaacaatg gctgagcata taaccatagg ttatggggaa caaaacaaca tcaaagtcac
                                                                        480
tgtatcaatt gccatgaaga cttgagggac ctgaatctac cgattcatct taaggcagca
                                                                        540
ggaccagttt gagtggcaac aatgcagcag cagaatcaat ggaaacaaca gaatgattgc
                                                                        600
aatgtccttt tttttctcct gcttctgact tgataaaagg ggaccgt
                                                                        647
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      <211> 460
      <212> DNA
      <213> Homo sapien
      <400> 309
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aatatgattg gctgcacact tccagactga tgaatgatga acgtgatgga ctattgtatg
                                                                        120
qaqcacatct tcagcaagag ggggaaatac tcatcatttt tggccagcag ttgtttgatc
                                                                        180
accaaacatc atgccagaat actcagcaaa ccttcttagc tcttgagaag tcaaagtccg
                                                                        240
ggggaattta ttcctggcaa ttttaattgg actccttatg tgagagcagc ggctacccag
                                                                        300
ctggggtggt ggagcgaacc cgtcactagt ggacatgcag tggcagagct cctggtaacc
                                                                        360
acctagagga atacacaggc acatgtgtga tgccaagcgt gacacctgta gcactcaaat
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                                                                          120
taggaaagag aaacacagaa ggaagagaca caataaaagt cattatgtat totgtgagaa
                                                                          180
gtcagacagt aagatttgtg ggaaatgggt tggtttgttg tatggtatgt attttagcaa
                                                                          240
taatotttat ggcagagaaa gotaaaatoo tttagottgo gtgaatgato acttgotgaa
                                                                          300
ttcctcaagg taggcatgat gaaggaggt ttagaggaga cacagacaca atgaactgac
                                                                          360
ctaqataqaa aqccttagta tactcagcta ggaatagtga ttctgagggc acactgtgac
                                                                          420
atgattatgt cattacatgt atggtagtga tggggatgat aggaaggaag aacttatggc
                                                                          480
atattttcac ccccacaaaa gtcagttaaa tattgggaca ctaaccatcc aggtcaaga
                                                                          539
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      <211> 526
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1)...(526)
      <223> n = A, T, C or G
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ttttgacgtt ttctctaaac tactaaagag gcattaatga tccataaatt atattatcta
                                                                          120
catttacage atttaaaatg tqttcageat gaaatattag ctacagggga agetaaataa
                                                                          180
                                                                          240
attaaacatg gaataaagat ttgtccttaa atataatcta caagaagact ttgatatttg
tttttcacaa gtgaagcatt cttataaagt gtcataacct ttttggggaa actatgggaa
                                                                          300
aaaatgggga aactctgaag ggttttaagt atcttacctg aagctacaga ctccataacc
                                                                          360
tetetttaca gggageteet geageeecta cagaaatgag tggetgagat tettgattge
                                                                          420
acagcaaqaq cttctcatct aaaccctttc cctttttagt atctgtgtat caagtataaa
                                                                          480
agttctataa actqtagtnt acttatttta atccccaaag cacagt
                                                                          526
      <210> 312
      <211> 500
      <212> DNA
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      <220>
      <221> misc feature
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      \langle 223 \rangle n = A, T, C or G
      <400> 312
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tcatttctga aagcagttga gccactttat tccaaagtac actgcagatg ttcaaactct
                                                                          120
ccatttetet ttecetteea eetgeeagtt ttgetgaete teaaettgte atgagtgtaa
                                                                          180
qcattaaqqa cattatqctt cttcgattct gaagacaggc cctgctcatg gatgactctg
                                                                          240
                                                                          300
gcttcttagg aaaatatttt tcttccaaaa tcagtaggaa atctaaactt atcccctctt
tgcagatgtc tagcagcttc agacatttgg ttaagaaccc atgggaaaaa aaaaaatcct
                                                                          360
tgctaatgtg gtttcctttg taaaccanga ttcttatttg nctggtatag aatatcagct ctgaacgtgt ggtaaagatt tttgtgtttg aatataggag aaatcagttt gctgaaaagt
                                                                          420
                                                                          480
                                                                          500
tagtettaat tatetattgg
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      <211> 718
      <212> DNA
      <213> Homo sapien
      <220>
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      <222> (1) ... (718)
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151

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atottcattt atototggcc ttaaccotgg ctcctgaggc tgcggccagc agatcccagg

ccagggctct gttcttgcca cacctgcttg a

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      <212> DNA
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gctgcaggct ggagtgtctt tattcctggc gggagaccgc acattccact gctgaggctg
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tgggggcggt ttatcaggca gtgataaaca t
                                                                        151
      <210> 319
      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 319
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                                                                         60
catagatagt actaggtatt aatagatatg taaagaaaga aatcacacca ttaataatgg
                                                                        120
taagattggg tttatgtgat tttagtgggt a .
                                                                        151
      <210> 320
      <211> 150
      <212> DNA
      <213> Homo sapien
      <400> 320
aactagtgga tocactagto cagtgtggtg gaattocatt gtgttggggt totagatogo
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gagcggctgc ccttttttt ttttttttg ggggggaatt ttttttttt aatagttatt
                                                                        120
gagtgttcta cagcttacag taaataccat
                                                                        150
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      <211> 151
      <212> DNA
      <213> Homo sapien
      <400> 321
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tagggtggca ttgtaaccag ctatggcata ggtgttaacc aaaggctgag taaacatggg
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tgcctctgag aaatcaaagt cttcatacac t
                                                                        151
      <210> 322
      <211> 151
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      <220>
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                                                                       120
attgtgcagg gctcgcttca nacttccagt t
                                                                       151
     <210> 323
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<222> (1)...(151)
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                                                                        60
nagactcant tactacccag tttgtggttt twtgggagaa atgtaactgg acagttagct
                                                                       120
gttcaatyaa aaagacactt ancccatgtg g
                                                                       151
      <210> 324
      <211> 461
      <212> DNA
      <213> Homo sapien
      <220>
      <221> misc feature
      <222> (1) ... (461)
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agaagtggtc agctaaagga atccaggttg ttggttggac tgttaatacc tttgatgaaa
                                                                       120
agagitacta cgaatccat cttggttcca gctatatcac tgacagcatg gtagaagact
                                                                       180
qcqaacctca cttctagact ttcacggtqq qacqaaacgg gttcagaaac tgccaggggc
                                                                       240
ctcatacagg gatatcaaaa taccctttgt gctacccagg ccctggggaa tcaggtgact
                                                                       300
cacacaaatg caatagttgg tcactgcatt tttacctgaa ccaaagctaa acccggtgtt
                                                                       360
gccaccatgc accatggcat gccagagttc aacactgttg ctcttgaaaa ttgggtctga
                                                                       420
aaaaacgcac aagagcccct gccctgccct agctgangca c
                                                                       461
      <210> 325
      <211> 400
      <212> DNA
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      <400> 325
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                                                                       120
agtaagagtg gtggcctatt tcagctgctt tgacaaaatg actggctcct gacttaacgt
                                                                       180
totataaatg aatgtgctga agcaaagtgc ccatggtggc ggcgaagaag agaaagatgt
                                                                       240
gttttgtttt ggactctctg tggtcccttc caatgctgtg ggtttccaac caggggaagg
                                                                       300
gtocottttg cattgocaag tgocataacc atgagcacta cgctaccatg gttotgocto
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ctggccaagc aggctggttt gcaagaatga aatgaatgat
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      <211> 1215
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                                                                       120
gaactectae accateggge tgggeetgea eagtettgag geegaceaag ageeagggag
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ccagatggtg gaggecagee teteogtacg geacceagag tacaacagae cettgetege
                                                                       240
                                                                       300
taacgacctc atgctcatca agttggacga atccgtgtcc gagtctgaca ccatccggag
catcagcatt gcttcgcagt gccctaccgc ggggaactct tgcctcgttt ctggctgggg
                                                                       360
tetgetggeg aaeggeagaa tgeetaeegt getgeagtge gtgaaegtgt eggtggtgte
                                                                       420
tgaggaggte tgcagtaage tetatgacee getgtaceae eecageatgt tetgegeegg
                                                                       480
cqqaqqqaa qaccaqaaqq actcctqcaa cqqtqactct qqqqqqccc tqatctqcaa
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egggtacttq caqqqccttq tqtctttcqq aaaaqccccq tqtqqccaag ttggcqtqcc
                                                                       600
aggtgtctac accaacctct gcaaattcac tgagtggata gagaaaaccg tccaggccag
                                                                       660
ttaactctgg ggactgggaa cccatgaaat tgacccccaa atacatcctg cggaaggaat
                                                                       720
traggaatat ctgttcccag ccctcctcc ctcaggccca ggagtccagg cccccagccc
                                                                       780
ctectecete aaaccaaqqq tacaqateee caqeeeetee teeteaqae ecaqqaqtee
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agaccecca gecetecte ecteagacee aggagtecag eccetecte etcagaceea ggagtecaga ecceceagee ecteeteet eagaceeagg ggtecaggee eccaaceet ecteecteag acteagagt ecaageeee aaceeteet teceeagace eagagteca ggtecaagee ecteeteet eagaceeage ggtecaatge eacetagaet etceetgtae acagtgeeee ettgtggeae gttgaceeaa ecttaceagt tggttttea tttttgtee ettteeeeta gateeagaaa taaagtetaa gagaagegea aaaaaaaaaa	900 960 1020 1080 1140 1200
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Leu Ser Ala Ala His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly 35 40	
Leu His Ser Leu Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu 50 55 60	
Ala Ser Leu Ser Val Arg His Pro Glu Tyr Asn Arg Pro Leu Leu Ala 65 70 75 80	
Asn Asp Leu Met Leu Ile Lys Leu Asp Glu Ser Val Ser Glu Ser Asp 85 90 95	
Thr Ile Arg Ser Ile Ser Ile Ala Ser Gln Cys Pro Thr Ala Gly Asn 100 105 110	
Ser Cys Leu Val Ser Gly Trp Gly Leu Leu Ala Asn Gly Arg Met Pro 115 120 125	
Thr Val Leu Gln Cys Val Asn Val Ser Val Val Ser Glu Glu Val Cys 130 135 140	
Ser Lys Leu Tyr Asp Pro Leu Tyr His Pro Ser Met Phe Cys Ala Gly 145 150 155 160	
Gly Gly Gln Asp Gln Lys Asp Ser Cys Asn Gly Asp Ser Gly Gly Pro 165 170 175	
Leu Ile Cys Asn Gly Tyr Leu Gln Gly Leu Val Ser Phe Gly Lys Ala 180 185 190	
Pro Cys Gly Gln Val Gly Val Pro Gly Val Tyr Thr Asn Leu Cys Lys 195 200 205	
Phe Thr Glu Trp Ile Glu Lys Thr Val Gln Ala Ser 210 215 220	
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<210> 329 <211> 77 <212> PRT <213> Homo sapien	`.
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Pro His Ser Gln Pro Trp Gln Ala Ala Leu Val Met Glu Asn Glu Leu
             20
                                  25
 Phe Cys Ser Gly Val Leu Val His Pro Gln Trp Val Leu Ser Ala Thr
                              40
                                                  45
 His Cys Phe Gln Asn Ser Tyr Thr Ile Gly Leu Gly Leu His Ser Leu
     50
                         55
                                              60
 Glu Ala Asp Gln Glu Pro Gly Ser Gln Met Val Glu Ala
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gctgcagcca
                                                                           70
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       <211> 22
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Gln His Asn Gly Pro Ile Pro Ser Leu Thr Pro Pro Ser Gly Ser Leu
 1
                 5
                                      10
Val Ser Gly Ser Cys Ser
             20
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                                                                          120
gtacatcaac tgttcagctt cctgggaaag tagttgtggt cacaggagct aatacaggta
                                                                         180
tegggaagga gacagecaaa gagetggete agagaggage tegagtatat ttagettgee
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gggatgtgga aaagggggaa ttggtggcca aagagatcca gaccacgaca gggaaccagc
                                                                          300
aggtgttggt gcggaaactg gacctgtctg atactaagtc tattcgagct tttgctaagg
                                                                         360
gettettage tgaggaaaag cacetecaeg ttttgateaa caatgeagga gtgatgatgt
                                                                         420
gtccgtactc gaagacagca gatggctttg agatgcacat aggagtcaac cacttqqqtc
                                                                         480
acttectect aacceatetg etgetagaga aactaaagga atcageecca teaaggatag
                                                                         540
taaatgtgtc ttccctcgca catcacctgg gaaggatcca cttccataac ctgcagggcg
                                                                         600
agaaatteta caatgeagge etggeetaet gteacageaa getageeaae ateetettea
                                                                         660
cccaggaact ggcccggaga ctaaaaggct ctggcgttac gacgtattct gtacaccctg
                                                                         720
gcacagtcca atctgaactg gttcggcact catctttcat gagatggatg tggtggcttt
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teteetttt cateaagaet eeteageagg gageeeagae eageetgeae tgtgeettaa
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cagaaggtet tgagatteta agtgggaate attteagtga etgteatgtg geatgggtet
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ctacacagta cttcttgtca aaatgattct ccttcaaggt tttcaaaacc tttagcacaa
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gaactagett etttgttcac aatteagtte eteccaacca accagtette actteaagag
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99

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                                                                      1740
                                                                      1800
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                                                                      1860
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1920
                                                                      1980
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                                                                      2040
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                                                                      2100
                                                                      2160
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ttgtttggag tgtgctattc taaaagattt tgatttcctg gaatgacaat tatattttaa ctttggtggg ggaaagagtt ataggaccac agtcttcact tctgatactt gtaaattaat
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                                                                      2460
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                                                                       540
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acagccagat gtgttgccag ggagaacaga acccaccagg tcccttttgg aaggcagcat
                                                                       780
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agttcatcac caaggacaag aggcgcaaga tctcggcagc caccagcctc tcggagcgcc
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Val Gln 1265 Asn Asn	Leu 1250 Glu Ile Glu	1235 Asp ) Asp Pro	Val Asn Glu Asp Lys 1300	Val Lys Cys Glu 1285 Leu	Lys Lys Ala 1270 Tyr Met	Leu Arg 1255 Leu Gly Ala	Leu 1240 Thr Met Asn	1225 Leu ) Ala Leu Thr Ala 1305	Asp Leu Leu Thr 1290 Leu	Arg Ile Glu 1275 Leu Leu	Arg Lys 1260 His His	Cys 1245 Ala ) Gly Tyr	1230 Gln Val Thr Ala Gly 1310	Leu Gln Asp Ile 1295 Ala	Asn Cys Pro 128 Tyr Asp
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Ser Asp Asp Glu Asp Asp Leu Gly Val Ala Pro Gly Leu Ala Pro Ala

85 90 95 Trp Ala Leu Thr Gln Pro Pro Ser Gln Ser Pro Gly Pro Gln Ser Leu 100 Pro Ser Thr Pro Ser Ser Ile Trp Pro Gln Trp Val Ile Leu Ile Thr Glu Leu Thr Ile Pro Ser Pro Ala His Gly Pro Pro Trp Leu Pro Asn Ala Leu Glu Arg Gly His Leu Val Arg Glu <210> 384 <211> 557 <212> DNA <213> Homo sapiens <400> 384 qqatcctcta gagcqqccqc ctactactac taaattcqcq gccqcqtcqa cqaaqaaqaq 60 aaagatgtgt tttgttttgg actctctgtg gtcccttcca atgctgtggg tttccaacca 120 ggggaagggt cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggt 180 tetgeeteet ggeeaageag getggtttge aagaatgaaa tgaatgatte tacagetagg 240 actiaacctt gaaatggaaa gtcttgcaat cccatttgca ggatccgtct gtgcacatgc 300 ctctgtagag agcagcattc ccagggacct tggaaacagt tggcactgta aggtgcttgc 360 tececaagae acateetaaa aggigitgta atggtgaaaa egtetteett etttattgee 420 cettettatt tatgtgaaca actgittgte ttittttgta tetttttaa actgtaaagt 480 tcaattqtqa aaatqaatat catqcaaata aattatqcqa tttttttttc aaagtaaaaa 540 aaaaaaaaaa aaaaaaa <210> 385 <211> 337 <212> DNA <213> Homo sapiens <400> 385 ttcccaqqtq atqtqcqaqq qaaqacacat ttactatcct tgatqqgqct gattccttta 60 gtttctctag cagcagatgg gttaggagga agtgacccaa gtggttgact cctatgtgca 120 teteaaagee atetgetgte ttegagtaeg gacacateat caeteetgea ttgttgatea 180 aaacgtggag gtgcttttcc tcagctaaga agcccttagc aaaagctcga atagacttag 240 tatcagacag gtocagttto ogcaccaaca cotgotggtt cootgtogtg gtotggatet 300 ctttggccac caattccccc ttttccacat cccggca <210> 386 <211> 300 <212> DNA <213> Homo sapiens <400> 386 gggcccgcta ccggcccagg ccccgcctcg cgagtcctcc tccccgggtg cctgcccgca 60 gcccgctcgg cccagagggt gggcgcgggg ctgcctctac cggctggcgg ctgtaactca 120 gcgaccttgg cccgaaggct ctagcaagga cccaccgacc ccagccgcgg cggcggcggc 180 gcggactttg cccggtgtgt ggggcggagc ggactgcgtg tccgcggacg ggcagcgaag 240 atgttageet tegetgeeag gaeegtggae egateeeagg getgtggtgt aaceteagee 300 <210> 387 <211> 537 <212> DNA <213> Homo sapiens

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 tgaaccagga ccggcttctg ggcggctgaa agggcaagg aggcaaggac cccgtctctc 180
 ccacggatgg ggagaggca ggaggagacc cagccaagtg ccttttcctc agcactgagg 240
gagggggett gtttcccttc cctcccggcg acaagctcca gggcagggct gtccctctgg 300
geggeceage acttecteag acacaactte tteetgetge tecagtegtg gggateatea 360
cttacccacc ccccaagttc aagaccaaat cttccagctg cccccttcgt gtttccctgt 420
gtttgctgta gctgggcatg tctccaggaa ccaagaagcc ctcagcctgg tgtagtctcc 480
ctgaccettg ttaatteett aagtetaaag atgatgaact teaaaaaaaa aaaaaaa
<210> 388
<211> 520
<212> DNA
<213> Homo sapiens
<400> 388
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gtttgaagat tgcctcttct acagcttctg agaattgtgt tatttcactt gccaagtgaa 180
ggaccccctc cccaacatgc cccagcccac ccctaagcat ggtcccttgt caccaggcaa 240
ccaggaaact gctacttgtg gacctcacca gagaccagga gggtttggtt agctcacagg 300
acttececca ecceagaaga ttageateee atactagaet catacteaac teaactagge 360
tcatactcaa ttgatggtta ttagacaatt ccatttcttt ctggttatta taaacagaaa 420
atctttcctc ttctcattac cagtaaaggc tcttggtatc tttctgttgg aatgatttct 480
atgaacttgt cttattttaa tggtgggttt tttttctggt
<210> 389
<211> 365
<212> DNA
<213> Homo sapiens
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cgttgcccca gtttgacaga aggaaaggcg gagcttattc aaagtctaga gggagtggag 60
gagttaagge tggattteag atetgeetgg tteeageege agtgtgeeet etgeteeece 120
aacgactttc caaataatct caccagegee ttecagetca ggegteetag aagegtettg 180
aageetatgg ceagetgtet ttgtgtteee teteaceege etgteeteae agetgagaet 240
cccaggaaac cttcagacta ccttcctctg ccttcagcaa ggggcgttgc ccacattctc 300
tgagggtcag tggaagaacc tagactccca ttgctagagg tagaaagggg aagggtgctg 360
gggag
<210> 390
<211> 221
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (221)
<223> n = A, T, C or G
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tgcctctcca tcctggcccc gacttctctg tcaggaaagt ggggatggac cccatctgca 60
tacacggntt ctcatgggtg tggaacatct ctgcttgcgg tttcaggaag gcctctggct 120
getetangag tetganenga ntegttgeee cantntgaca naaggaaagg eggagettat 180
tcaaagtcta gagggagtgg aggagttaag gctggatttc a
<210> 391
<211> 325
<212> DNA
<213> Homo sapiens
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<220>
<221> misc feature
<222> (1)...(325)
<223> n = A, T, C or G
<400> 391
tggagcaggt cccgaggcct ccctagagcc tggggccgac tctgtgncga tgcangcttt 60
ctctcgcgcc cagcctggag ctgctcctgg catctaccaa caatcagncg aggcgagcag 120
tagecaggge actgetgeea acagecagte ennataceat catginacee ggtgngetet 180
naanttngat ntccanagee etacecaten tagttetget eteccacegg ntaccageee 240
cactgoccag gaatcotaca gocagtacco tgtoccgacg tototacota ccagtacgat 300
gagaceteeg getactaeta tgace
<210> 392 -
<211> 277
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(277)
<223> n = A, T, C or G
<400> 392
atattqttta actecttect ttatatettt taacatttte atggngaaag gttcacatet 60
agtotoactt nggcnagngn ctcctacttg agtotottoc ccggcctgnn ccagtngnaa 120
antaccanga accgncatgn cttaanaacn ncctggtttn tgggttnntc aatgactgca 180
tgcagtgcac caccetgtce actacgtgat getgtaggat taaagtetea cagtgggegg 240
ctgaggatac agcgccgcgt cctgtgttgc tggggaa
<210> 393
<211> 566
<212> DNA
<213> Homo sapiens
<400> 393
actagtccag tgtggtggaa ttcgcggccg cgtcgacgga caggtcagct gtctggctca 60
gtgatctaca ttctgaagtt gtctgaaaat gtcttcatga ttaaattcag cctaaacgtt 120
ttgccgggaa cactgcagag acaatgctgt gagtttccaa ccttagccca tctgcgggca 180
gagaaggtot agtttgtoca toagoattat catgatatoa ggactggtta cttggttaag 240
gaggggtcta ggagatctgt cccttttaga gacaccttac ttataatgaa gtatttggga 300
gggtggtttt caaaagtaga aatgteetgt atteegatga teateetgta aacattttat 360
catttattaa tcatccctgc ctgtgtctat tattatattc atatctctac gctggaaact 420
cattetetge etgagtttta atttttgtee aaagttattt taatetatae aattaaaage 540
ttttgcctat caaaaaaaa aaaaaa
<210> 394
<211> 384
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(384)
<223> n = A, T, C or G
<400> 394
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tgcaaattng gaccgggcca aggctggact gctggagcgt gtgaaggagc tacaggccna 120
gcaggaggac cgggctttaa ggagttttaa gctgagtgtc actgtagacc ccaaatacca 180
tcccaagatt atcgggagaa agggggcagt aattacccaa atccggttgg agcatgacgt 240
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```
gaacatccag tttcctgata aggacgatgg gaaccagece caggaccaaa ttaccatcac 300
 agggtacgaa aagaacacag aagctgccag ggatgctata ctgagaattg tgggtgaact 360
 tgagcagatg gtttctgagg acgt
 <210> 395
 <211> 399
 <212> DNA
 <213> Homo sapiens
 <400> 395
 ggcaaaactg tgtgacctca ataagacctc gcagatccaa ggtcaagtat cagaagtgac 60
 totgacettg gactocaaga cotacatcaa cagootggot atattagatg atgagocagt 120
 tatcagaggt ttcatcattg cggaaattgt ggagtctaag gaaatcatgg cctctgaagt 180
attcacgtct ttccagtacc ctgagttctc tatagagttg cctaacacag gcagaattgg 240
ccagetactt gtctgcaatt gtatetteaa gaataceetg gecateeett tgactgaegt 300
caagttetet ttggaaagee tgggeatete eteactacag acetetgace atgggaeggt 360
gcagcctggt gagaccatcc aatcccaaat aaaatgcac
                                                                     399
<210> 396
<211> 403
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (403)
<223> n = A, T, C or G
<400> 396
tggagttntc agtgcaaaca agccataaag cttcagtagc aaattactgt ctcacagaaa 60
gacattttca acttctgctc cagctgctga taaaacaaat catgtgttta gcttgactcc 120
agacaaggac aacctgttcc ttcataactc tctagagaaa aaaaggagtt gttagtagat 180
actaaaaaaa gtggatgaat aatctggata tttttcctaa aaagattcct tqaaacacat 240
taggaaaatg gagggcctta tgatcagaat gctagaatta gtccattgtg ctgaagcagg 300
gtttagggga gggagtgagg gataaaagaa ggaaaaaaag aagagtgaga aaacctattt 360
atcaaagcag gtgctatcac tcaatgttag gccctgctct ttt
                                                                     403
<210> 397
<211> 100
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(100)
<223> n = A, T, C or G
<400>:397
actagincag igiggiggaa ticgcggccg cgicgaccia naanccatci ciatagcaaa 60
tccatccccg ctcctggttg gtnacagaat gactgacaaa
<210> 398 <211> 278
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (278)
<223> n = A,T,C or G
<400> 398
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geggeegegt egacageagt teegeeageg etegeeeetg ggtggggatg tgetgeaege 60
ccacctggac atctggaagt cagcggcctg gatgaaagag cggacttcac ctggggcgat 120
teactactgt geetegacea gtgaggagag etggaeegae agegaggtgg aeteateatg 180
ctccgggcag cccatccacc tgtggcagtt cctcaaggag ttgctactca agccccacag 240
ctatggccgc ttcattangt ggctcaacaa ggagaagg
<210> 399
<211> 298
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(298)
<223> n = A, T, C or G
<400> 399
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ggggtgccng catggagcgc atgggcgcgg qcctgggcca cggcatggat cgcgtqqqct 120
ccgagatcga gcgcatgggc ctggtcatgg accgcatggg ctccgtggag cgcatgggct 180
ceggeattga gegeatggge cegetgggee tegaceaeat ggeeteeane attganegea 240
tgggccaqac catqgaqcqc attqqctctq qcqtqqaqcn catqqqtqcc qqcatqqq
<210> 400
<211> 548
<212> DNA
<213> Homo sapiens
<400> 400
acatcaacta cttcctcatt ttaaggtatg gcagttccct tcatcccctt ttcctgcctt 60
gtacatgtac atgtatgaaa tttccttctc ttaccgaact ctctccacac atcacaaggt 120
tgagtctctt ttttccacgt ttaaggggcc atggcaggac ttagagttgc gagttaagac 240
tgcagagggc tagagaatta tttcatacag gctttgaggc cacccatgtc acttatcccg 300
tataccetet caccatecce ttgtetacte tgatgeecce aagatgeaac tgggeageta 360
gttggcccca taattctggg cctttgttgt ttgttttaat tacttgggca tcccaggaag 420
etttecagtg atetectace atgggeeece etectgggat caageeecte ceaggeeetg 480
tecccagece etectgeece ageceaeceg ettgeettgg tgeteagece teccattggg 540
agcaggtt
                                                                 548
<210> 401
<211> 355
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (355)
<223> n = A,T,C or G
<400> 401
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tgatgtctcc aagtagtcca ccttcattta actctttgaa actgtatcat ctttgccaag 120
taagagtggt ggcctatttc agctgctttg acaaaatgac tggctcctga cttaacgttc 180
tataaatgaa tgtgctgaag caaagtgccc atggtggcgg cgaagaagan aaagatgtgt 240
tttgttttgg actctctgtg gtcccttcca atgctgnggg tttccaacca ggggaagggt 300
cccttttgca ttgccaagtg ccataaccat gagcactact ctaccatggn tctgc
<210> 402
<211> 407
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1) ... (407)
<223> n = A, T, C or G
<400> 402
atggggcaag ctggataaag aaccaagacc cactggagta tgctgtcttc aagaaaccca 60
tctcacatgc ggtggcatac ataggctcaa aataaaggaa tggagaaaaa tatttcaagc 120
aaatggaaaa cagaaaaaag caggtgttgc actcctactt tctgacaaaa cagactatgc 180
gaataaagat aaaaaagaga aggacattac aaaggtggtc ctgacctttg ataaatctca 240
ttgcttgata ccaacctggg ctgttttaat tgcccaaacc aaaaggataa tttgctqaqq 300
ttgtggaget teteceetge agagagteee tgateteeea aaatttggtt gagatgtaag 360
gntgattttg ctgacaactc cttttctgaa gttttactca tttccaa
<210> 403
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
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<223>.n = A,T,C \text{ or } G
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cagtatttat agccnaactg aaaagctagt agcaggcaag totcaaatcc aggcaccaaa 60
tcctaagcaa gagccatggc atggtgaaaa tgcaaaagga gagtctggcc aatctacaaa 120
tagagaacaa gacctactca gtcatgaaca aaaaggcaga caccaacatg gatctcatgg 180
gggattggat attgtaatta tagagcagga agatgacagt gatcgtcatt tggcacaaca 240
tettaacaac gaccgaaacc cattatttac ataaacctcc atteggtaac catgttgaaa 300
gga
<210> 404
<211> 225
<212> DNA
<213> Homo sapiens
<400> 404
aagtgtaact tttaaaaatt tagtggattt tgaaaattct tagaggaaag taaaggaaaa 60
attgttaatg cactcattta cctttacatg gtgaaagttc tctcttgatc ctacaaacag 120
acattttcca ctcgtgtttc catagttgtt aagtgtatca gatgtgttgg gcatgtgaat 180
ctccaagtgc ctgtgtaata aataaagtat ctttatttca ttcat
<210> 405
<211> 334
<212> DNA
<213> Homo sapiens .
<220>
<221> misc_feature
<222> (1) ... (334)
<223> n = A, T, C or G
<400> 405
gagetgttat actgtgagtt ctactaggaa atcatcaaat ctgagggttg tctggaggac 60
ttcaatacac ctccccccat agtgaatcag cttccagggg gtccagtccc tctccttact 120
tcatccccat cccatgccaa aggaagaccc tccctccttg gctcacagcc ttctctaggc 180
ttcccagtgc ctccaggaca gagtgggtta tgttttcagc tccatccttg ctqtqaqtqt 240
ctggtgcggt tgtgcctcca gcttctgctc agtgcttcat ggacagtgtc cagcccatgt 300
cactetecae teteteanng tggateceae eeet
                                                                   334
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<210> 406
<211> 216
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (216)
<223> n = A, T, C or G
<400> 406
tttcatacct aatgagggag ttganatnac atnnaaccag gaaatgcatg gatctcaang 60
gaaacaaaca cccaataaac tcggagtggc agactgacaa ctgtgagaca tgcacttgct 120
acnaaacaca aatttnatgt tgcacccttg tttctacacc tgtgggttat gacaaagaca 180
actgccaaag aatnttcaag aaggaggact gccant
<210> 407
<211> 413
<212> DNA
<213> Homo sapiens
<400> 407
gctgacttgc tagtatcatc tgcattcatt gaagcacaag aacttcatgc cttgactcat 60
gtaaatgcaa taggattaaa aaataaattt gatatcacat ggaaacagac aaaaaatatt 120
gtacaacatt gcacccagtg tcagattcta cacctggcca ctcaggaagc aagagttaat 180
eccagaggte tatgteetaa tgtgttatgg caaatggatg teatgeaegt acetteattt 240
ggaaaattgt catttgtcca tgtgacagtt gatacttatt cacatttcat atgggcaacc 300
tgccagacag gagaaagtct tcccatgtta aaagacattt attatcttgt tttcctgtca 360
tgggagttcc agaaaaagtt aaaacagaca atgggccagg ttctgtagta aag
<210> 408
<211> 183
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(183)
<223> n = A, T, C or G
<400> 408
ggagetngcc ctcaattcct ccatntctat gttancatat ttaatgtctt ttgnnattaa 60
tncttaacta gttaatcctt aaagggctan ntaatcctta actagtccct ccattgtgag 120
cattateett eeagtatten eettetnttt tatttaetee tteetggeta eeeatgtaet 180
ntt
<210> 409
<211> 250
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (250)
<223> n = A,T,C or G
<400> 409
cccacgcatg ataagctctt tatttctgta agtcctgcta ggaaatcatc aaatctgacg 60
gtggtttggg ggacctgaac aaacctcctg taattaatca gctttcagtt tctccccta 120
gtccctcctt caacaacata ggaggatcct ccccttcttt ctgctcacgg ccttatctag 180
getteecagt geeceeagga eagegtggge tatgtttaea gegenteett getggggggg 240
ggccntatgc
```

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<210> 410
<211> 306
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (306)
<223> n = A, T, C or G
<400> 410
ggctggtttg caagaatgaa atgaatgatt ctacagctag gacttaacct tgaaatggaa 60
agtetigeaa teccattige aggateegte tgtgeacatg eetetgtaga gageageatt 120
cccagggacc ttggaaacag ttggcactgt aaggtgcttg ctccccaaga cacatcctaa 180
aaggtgttgt aatggtgaaa accgcttcct tctttattgc cccttcttat ttatgtgaac 240
nactggttgg ctttttttgn atctttttta aactggaaag ttcaattgng aaaatgaata 300
tentge
<210> 411
<211> 261
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(261)
<223> n = A, T, C or G
<400> 411
agagatattn cttaggtnaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatcttttg tatttaagga ttctgagatt ttgcttgagc aggattagat aaggctgttc 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat cagttccagc 240
cttctctcaa qqnqaqqcaa a
<210> 412
<211> 241
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(241)
<223> n = A, T, C \text{ or } G
<400> 412
gttcaatgtt acctgacatt tctacaacac cccactcacc gatgtattcg ttgcccagtg 60
ggaacatacc agcctgaatt tggaaaaaat aattgtgttt cttgcccagg aaatactacg 120
actgactttg atggctccac aaacataacc cagtgtaaaa acagaagatg tggaggggag 180
ctgggagatt tcactgggta cattgaattc ccaaactacc cangcaatta cccagccaac 240
                                                                    241
<210> 413
<211> 231
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (231)
<223> n = A, T, C or G
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<400> 413
aactcttaca atccaagtga ctcatctgtg tgcttgaatc ctttccactg tctcatctcc 60
ctcatccaag tttctagtac cttctctttg ttgtgaagga taatcaaact gaacaacaaa 120
aagtttactc tecteatttg gaacetaaaa actetettet teetgggtet gagggeteea 180
agaatcottg aatcanttot cagatcattg gggacaccan atcaggaacc t
<210> 414
<211> 234
<212> DNA
<213> Homo sapiens
<400> 414
actgtccatg aagcactgag cagaagctgg aggcacaacg caccagacac tcacagcaag 60
gatggagetg aaaacataac ccactetgte etggaggeac tgggaageet agagaagget 120
gtgagccaag gagggagggt cttcctttgg catgggatgg ggatgaagta aggagaggga 180
ctggaccccc tggaagctga ttcactatgg ggggaggtgt attgaagtcc tcca
<210> 415
<211> 217
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(217)
<223> n = A, T, C or G
<400> 415
qcataggatt aagactgagt atcttttcta cattctttta actttctaag gggcacttct 60
caaaacacag accaggtage aaateteeac tgetetaagg nteteaceac caetttetea 120
cacctagcaa tagtagaatt cagtcctact tctgaggcca gaagaatggt tcagaaaaat 180
antggattat aaaaaataac aattaagaaa aataatc
<210> 416
<211> 213
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(213)
<223> n = A, T, C or G
<400> 416
atgcatatnt aaagganact gcctcgcttt tagaagacat ctggnctgct ctctgcatga 60
ggcacagcag taaagctctt tgattcccag aatcaagaac tctccccttc agactattac 120
cgaatgcaag gtggttaatt gaaggccact aattgatgct caaatagaag gatattgact 180
atattggaac agatggagtc tctactacaa aag
<210> 417
<211> 303
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(303)
<223> n = A, T, C or G
<400> 417
nagtottcag gcccatcagg gaagttcaca ctggagagaa gtcatacata tgtactgtat 60
```

```
gtgggaaagg ctttactctg agttcaaatc ttcaagccca tcagagagtc cacactggag 120
 agaagccata caaatgcaat gagtgtggga agagcttcag gagggattcc cattatcaag 180 ttcatctagt ggtccacaca ggagagaaac cctataaatg tgagatatgt gggaagggct 240
 tcantcaaag ttcgtatctt caaatccatc ngaaggncca cagtatanan aaacctttta 300
 <210> 418
 <211> 328
 <212> DNA
 <213> Homo sapiens
 <220>
 <221> misc feature
 <222> (1) ... (328)
 <223> n = A, T, C or G
<400> 418
tttttggcgg tggtggggca gggacgggac angagtctca ctctgttgcc caggctggag 60
tgcacaggca tgatctcggc tcactacaac ccctgcctcc catgtccaag cgattcttgt 120
gcctcagcct tccctgtagc tagaattaca ggcacatgcc accacaccca gctagttttt 180
gtatttttag tagagacagg gtttcaccat gttggccagg ctggtctcaa actcctnacc 240
teagnggtea ggetggtete aaacteetga ceteaagtga tetgeceace teageeteee 300
aaagtgctan gattacaggc cgtgagcc
<210> 419
<211> 389
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(389)
<223> n = A, T, C or G
<400> 419
cctcctcaag acggcctgtg gtccgcctcc cggcaaccaa gaagcctgca gtgccatatg 60
accectgage catggactgg agectgaaag geagegtaca eeetgeteet gatettgetg 120
cttgtttcct ctctgtggct ccattcatag cacagttgtt gcactgaggc ttgtgcaggc 180
cgagcaaggc caagctggct caaagagcaa ccagtcaact ctgccacggt gtgccaggca 240
coggittetec agecaccaac etcactoget ecogeaaatg geacateagt tettetacee 300
taaaggtagg accaaagggc atctgctttt ctgaagtcct ctgctctatc agccatcacg 360
tggcagccac tcnggctgtg tcgacgcgg
<210> 420
<211> 408
<212> DNA
<213> Homo sapiens
<400> 420
gtteeteeta aeteetgeea gaaacagete teeteaacat gagagetgea eeeeteetee 60
tqqccaqqqc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180 gtcccattga cacctttccc actgaccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cgaagcacag 360
acqttgaccg gactttgatg aagtgctatg acaaacctgg caagcccg
<210> 421
<211> 352
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc_feature
<222> (1) ... (352)
<223> n = A, T, C or G
gctcaaaaat ctttttactg atnggcatgg ctacacaatc attgactatt acggaggcca 60
gaggagaatg aggcctggcc tgggagccct gtgcctacta naagcacatt agattatcca 120
ttcactgaca gaacaggtct tttttgggtc cttcttctcc accacnatat acttgcagtc 180
ctccttcttg aagattcttt ggcagttgtc tttgtcataa cccacaggtg tagaaacaag 240
ggtgcaacat gaaatttctg tttcgtagca agtgcatgtc tcacaagttg gcangtctgc 300
cactocgagt ttattgggtg tttgtttcct ttgagatcca tgcatttcct gg
<210> 422
<211> 337
<212> DNA
<213> Homo sapiens
<400> 422
atgccaccat gctggcaatg cagcgggcgg tcgaaggcct gcatatccag cccaagctgg 60
cgatgatcga cggcaaccgt tgcccgaagt tgccgatgcc agccgaagcg gtggtcaagg 120
gcgatagcaa ggtgccggcg atcgcggcgg cgtcaatcct ggccaaggtc agccgtgatc 180
gtgaaatggc agctgtcgaa ttgatctacc cgggttatgg catcggcggg cataagggct 240
atccgacacc ggtgcacctg gaagccttgc agcggctggg gccgacgccg attcaccgac 300
gcttcttccg ccggtacggc tggcctatga aaattat
<210> 423
<211> 310
<212> DNA
<213> Homo sapiens
<221> misc_feature
<222> (1)...(310)
<223> n = A, T, C or G
<400> 423
qctcaaaaat ctttttactg atatggcatg gctacacaat cattgactat tagaggccag 60
aggagaatga ggcctggcct gggagccctg tgcctactan aagcncatta gattatccat 120
teactgacag aacaggtett tittgggtee tietteteea ceacgatata ettgeagtee 180
teettettga agattetttg geagttgtet ttgteataac ceacaggtgt anaaacaagg 240
gtgcaacatg aaatttetgt ttegtageaa gtgcatgtet cacagttgte aagtetgeec 300
tccgagttta
                                                                   310
<210> 424
<211> 370
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(370)
<223> n = A, T, C or G
<400> 424
gctcaaaaat ctttttactg ataggcatgg ctacacaatc attgactatt agaggccaga 60
qqaqaatqaq qcctqqcctg qqaqccctgt qcctactaqa aqcacattag attatccatt 120
cactgacaga acaggtettt tttgggteet tetteteeae cacgatatae ttgeagteet 180
ccttcttgaa gattctttgg cagttgtctt tgtcataacc cacaggtgta gaaacatcct 240
qqttqaatct cctggaactc cctcattagg tatgaaatag catgatgcat tgcataaagt 300
cacgaaggtg gcaaagatca caacgctgcc cagganaaca ttcattgtga taagcaggac 360
tccgtcgacg
```

```
<210> 425
<211> 216
<212> DNA
<213> Homo sapiens
<221> misc feature
<222> (1) ... (216)
<223> n = A, T, C or G
<400> 425
taacaacnca acatcaaggn aaananaaca ggaatggntg actntgcata aatnqqccqa 120
anattateca ttatnttaag ggttgaette aggntacage acacagaeaa acatgeecag 180
gaggntntca ggaccgctcg atgtnttntg aggagg
                                                                    216
<210> 426
<211> 596
<212> DNA
<213> Homo sapiens
<400> 426
cttccagtga ggataaccct gttgccccgg gccgaggttc tccattaggc tctgattgat 60
tggcagtcag tgatggaagg gtgttctgat cattccgact gccccaaggg tcqctggcca 120
gctctctgtt ttgctgagtt ggcagtagga cctaatttgt taattaagag tagatggtga 180
getgteettg tattttgatt aacctaatgg cetteecage acgaetegga tteagetqga 240
gacatcacgg caacttttaa tgaaatgatt tgaaqqqcca ttaaqaqqca cttcccqtta 300
ttaggcagtt catctgcact gataacttct tggcagctga qctqqtcqqa qctqtqqccc 360
aaacgcacac ttggcttttg gttttgagat acaactctta atcttttagt catgcttgag 420 ggtggatggc cttttcagct ttaacccaat ttgcactgcc ttggaagtgt agccaggaga 480
atacactcat atactcgtgg gcttagaggc cacagcagat gtcattggtc tactgcctga 540
gtecegetgg teceatecea ggacetteca teggegagta eetgggagee eqtqet
<210> 427
<211> 107
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (107)
<223> n = A, T, C or G
<400> 427
gaagaattca agttaggttt attcaaaggg cttacngaga atcctanacc caggncccag 60
cccgggagca gccttanaga gctcctgttt gactgcccgg ctcagng
                                                                   107
<210> 428
<211> 38
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(38)
<223> n = A, T, C or G
<400> 428
gaacttccna anaangactt tattcactat tttacatt
                                                                   38
<210> 429
```

```
<211> 544
<212> DNA
<213> Homo sapiens
<400> 429
ctttgctgga cggaataaaa gtggacgcaa gcatgacctc ctgatgaggg cgctgcattt 60
attgaagage ggetgeagee etgeggttea gattaaaate egagaattgt atagaegeeg 120
atatecaega actettgaag gaetttetga tttatecaea ateaaateat eggtttteag 180
tttggatggt ggctcatcac ctgtagaacc tgacttggcc gtggctggaa tccactcgtt 240
geetteeact teagttaeae eteaeteaee ateeteteet gttggttetg tgetgettea 300
agatactaag cccacatttg agatgcagca gccatctccc ccaattcctc ctgtccatcc 360
tgatgtgcag ttaaaaaatc tgccctttta tgatgtcctt gatgttctca tcaagcccac 420
gagtttagtt caaagcagta ttcagcgatt tcaagagaag ttttttattt ttgctttgac 480
acctcaacaa gttagagaga tatgcatatc cagggatttt ttgccaggtg gtaggagaga 540
ttat
<210> 430
<211> 507
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (507)
<223> n = A, T, C or G
<400> 430
cttateneaa tggggeteee aaacttgget gtgeagtgga aacteegggg gaattttgaa 60
gaacactgac accoatcttc caccecgaca ctetgattta attgggetge agtgagaaca 120
qaqcatcaat ttaaaaaqct gcccagaatg ttntcctqqg cagcgttgtg atctttgccn 180
ccttcgtgac tttatgcaat gcatcatgct atttcatacc taatgaggga gttccaggag 240
attcaaccag gatgtttcta cncctgtggg ttatgacaaa gacaactgcc aaagaatntt 300
caagaaggag gactgcaagt atatcgtggt ggagaagaag gacccaaaaa agacctgttc 360 tgtcagtgaa tggataatct aatgtgcttc tagtaggcac agggctccca ggccaggcct 420
catteteete tggeetetaa tagteaatga ttgtgtagee atgeetatea gtaaaaagat 480
ttttgagcaa aaaaaaaaa aaaaaaa
<210> 431
<211> 392
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1) ... (392)
<223> n = A, T, C or G
<400> 431
gaaaattcag aatggataaa aacaaatgaa gtacaaaata tttcagattt acatagcgat 60
aaacaagaaa gcacttatca qqaqqactta caaatggaag tacactctan aaccatcatc 120
tatcatggct aaatgtgaga ttagcacagc tgtattattt gtacattgca aacacctaga 180
aagagatggg aaacaaaatc ccaggagttt tgtgtgtgga gtcctgggtt ttccaacaga 240
catcattcca gcattctgag attagggnga ttggggatca ttctggagtt ggaatgttca 300
acaaaagtga tgttgttagg taaaatgtac aacttctgga tctatgcaga cattgaaggt 360
                                                                      392
gcaatgagtc tggcttttac tctgctgttt ct
<210> 432
<211> 387
<212> DNA
<213> Homo sapiens
<220>
```

```
<221> misc feature
 <222> (1)...(387)
 <223> n = A, T, C or G
 <400> 432
ggtatccnta cataatcaaa tatagctgta gtacatgttt tcattggngt agattaccac 60
aaatgcaagg caacatgtgt agatetettg tettattett ttgtetataa taetgtattg 120
ngtagtccaa gctctcggna gtccagccac tgngaaacat gctcccttta gattaacctc 180
gtggaeneth ttgttgnatt gtetgaactg tagngeeetg tattttgett etgtetgnga 240
attetgttgc ttetggggca ttteettgng atgeagagga ceaceacaca gatgacagea 300
atctgaattg ntccaatcac agctgcgatt aagacatact gaaatcgtac aggaccggga 360
acaacgtata gaacactgga gtccttt
<210> 433
<211> 281
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(281)
<223> n = A, T, C or G
<400> 433
ttcaactagc anagaanact gcttcagggn gtgtaaaatg aaaggcttcc acgcagttat 60
ctgattaaag aacactaaga gagggacaag gctagaagcc gcaggatgtc tacactatag 120
caggenetat ttgggttgge tggaggaget gtggaaaaca tggagagatt ggegetggag 180
ategoogtgg ctattecten ttgntattac accagngagg ntetetgtnt geccaetqqt 240
tnnaaaaccg ntatacaata atgatagaat aggacacaca t
                                                                   281
<210> 434
<211> 484
<212> DNA
<213> Homo sapiens
<400> 434
ttttaaaata agcatttagt gctcagtccc tactgagtac tctttctctc ccctcctctq 60
aatttaattc titcaacttg caatttgcaa ggattacaca titcactgtg atgtatattg 120
tgttgcaaaa aaaaaaaagt gtctttgttt aaaattactt ggtttgtgaa tccatcttgc 180
tttttcccca ttggaactag tcattaaccc atctctgaac tggtagaaaa acatctgaag 240
agctagtcta tcagcatctg acaggtqaat tqqatqqttc tcagaaccat ttcaccaga 300
cagoctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca taacaaaccc 360
tgctccaatc tgtcacataa aagtctgtga cttgaagttt agtcagcacc cccaccaaac 420
tttatttttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataaag tacccatgtc 480
ttta
                                                                   484
<210> 435
<211> 424
<212> DNA
<213> Homo sapiens
<400> 435
gegeegetea gageaggtea etttetgeet tecaegteet eetteaagga ageeeeatgt 60
gggtagettt caatategea ggttettaet cetetgeete tataagetea aacceaceaa 120
cgatcgggca agtaaacccc ctccctcgcc gacttcggaa ctggcgagag ttcagcgcag 180
atgggcctgt ggggaggggg caagatagat gagggggagc ggcatggtgc ggggtgaccc 240
cttggagaga ggaaaaaggc cacaagaggg gctgccaccg ccactaacgg agatggccct 300
ggtagagacc tttgggggtc tggaacctct ggactcccca tgctctaact cccacactct 360
gctatcagaa acttaaactt gaggattttc tctgtttttc actcgcaata aattcagagc 420
aaac
```

```
<211> 667
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(667)
<223> n = A, T, C or G
<400> 436
accttgggaa nactctcaca atataaaggg tcgtagactt tactccaaat tccaaaaagg 60
tectggecat gtaateetga aagtttteee aaggtageta taaaateett ataagggtge 120
agcetettet ggaatteete tgattteaaa gteteactet caagttettg aaaacgaggg 180
cagtteetga aaggeaggta tageaactga tetteagaaa gaggaactgt gtgeaceggg 240
atgggctgcc agagtaggat aggattccag atgctgacac cttctggggg aaacagggct 300
gccaggtttg tcatagcact catcaaagtc cggtcaacgt ctgtgcttcg aatataaacc 360
tgttcatgtt tataggactc attcaagaat tttctatatc tctttcttat atactctcca 420
agttcataat gctgctccat gcccagctgg gtgagttggc caaatccttg tggccatgag 480
gatteettta tggggteagt gggaaaggtg teaatgggae tteggtetee atgeegaaac 540
accaaagtca caaacttcaa ctccttggct agtacacttc ggtctagcca gaaaaaaagc 600
agaaacaaga agccaaggct aaggcttgct gccctgccag gaggaggggt gcagctctca 660
tgttgag
<210> 437
<211> 693
<212> DNA
<213> Homo sapiens
<400> 437
ctacqtctca accctcattt ttaqqtaaqq aatcttaaqt ccaaaqatat taaqtqactc 60
acacagocag gtaaggaaag ctggattggc acactaggac totaccatac cgggttttgt 120
taaageteag gttaggagge tgataagett ggaaggaact teagacaget tttteagate 180
ataaaagata attottagcc catgttotto tocagagoag acctgaaatg acagcacagc 240
aggtactect ctatttteac ecetettget tetactetet ggeagteaga eetgtgggag 300
gccatgggag aaagcagctc tctggatgtt tgtacagatc atggactatt ctctgtggac 360
cattleteca ggttacceta ggtgtcacta ttggggggac agccagcate tttagettte 420
atttgagttt ctgtctgtct tcagtagagg aaacttttgc tcttcacact tcacatctga 480
acacctaact gctgttgctc ctgaggtggt gaaagacaga tatagagctt acagtattta 540
tcctatttct aggcactgag ggctgtgggg taccttgtgg tgccaaaaca gatcctgttt 600
taaggacatg ttgcttcaga gatgtctgta actatctggg ggctctgttg gctctttacc 660
ctgcatcatg tgctctcttg gctgaaaatg acc
<210> 438
<211> 360
<212> DNA
<213> Homo sapiens
<400> 438
ctgcttatca caatgaatgt tctcctgggc agcgttgtga tctttgccac cttcgtgact 60
ttatgcaatg catcatgcta tttcatacct aatgagggag ttccaggaga ttcaaccagg 120
atgtttctac acctgtgggt tatgacaaag acaactgcca aagaatcttc aagaaggagg 180
actgcaagta tatctggtgg agaagaagga cccaaaaaaag acctgttctg tcagtgaatg 240
gataatetaa tgtgetteta gtaggeacag ggeteecagg ceaggeetea tteteetetg 300
gcctctaata gtcaataatt gtgtagccat gcctatcagt aaaaagattt ttgagcaaac 360
<210> 439
<211> 431
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
```

```
<222> (1)...(431)
<223> n = A, T, C or G
<400> 439
gttcctnnta actcctgcca gaaacagctc tcctcaacat gagagctqca cccctcctcc 60
tggccagggc agcaagcctt agccttggct tcttgtttct gctttttttc tggctagacc 120
gaagtgtact agccaaggag ttgaagtttg tgactttggt gtttcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cqaaqcacaq 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag t
<210> 440
<211> 523
<212> DNA
<213> Homo sapiens
<400> 440
agagataaag cttaggtcaa agttcataga gttcccatga actatatgac tggccacaca 60
ggatettttg tatttaagga ttetgagatt ttgettgage aggattagat aaggetgtte 120
tttaaatgtc tgaaatggaa cagatttcaa aaaaaaaccc cacaatctag ggtgggaaca 180
aggaaggaaa gatgtgaata ggctgatggg caaaaaacca atttacccat caqttccaqc 240
cttctctcaa ggagaggcaa agaaaggaga tacagtggag acatctggaa agttttctcc 300
actggaaaac tgctactatc tgtttttata tttctgttaa aatatatgag gctacagaac 360
taaaaattaa aacctctttg tgtcccttgg tcctggaaca tttatgttcc ttttaaagaa 420
acaaaaatca aactttacag aaagatttga tgtatgtaat acatatagca gctcttgaag 480
                                                                   523
tatatatatc atagcaaata agtcatctga tgagaacaag cta
<210> 441
<211> 430
<212> DNA
<213> Homo sapiens
<400> 441
gttcctccta actcctgcca gaaacagctc tcctcaacat gagagctgca cccctcctcc 60
tggccagggc agcaagcett agcettgget tettgtttet getttttte tggctagace 120
gaagtgtact agccaaggag tigaagiitg tgaciitggt gittcggcat ggagaccgaa 180
gtcccattga cacctttccc actgacccca taaaggaatc ctcatggcca caaggatttg 240
gccaactcac ccagctgggc atggagcagc attatgaact tggagagtat ataagaaaga 300
gatatagaaa attottgaat gagtootata aacatgaaca ggtttatatt cgaagcacag 360
acgttgaccg gactttgatg agtgctatga caaacctggc agcccgtcga cgcggccgcg 420
aatttagtag
                                                                   430
<210> 442
<211> 362
<212> DNA
<213> Homo sapiens
<400> 442
ctaaggaatt agtagtgttc ccatcacttg tttggagtgt gctattctaa aagattttga 60
tttcctggaa tgacaattat attttaactt tggtgggga aagagttata ggaccacagt 120
cttcacttct gatacttgta aattaatctt ttattgcact tgttttgacc attaagctat 180
atgtttagaa atggtcattt tacggaaaaa ttagaaaaat tctgataata gtgcagaata 240
aatgaattaa tgitttactt aattiatatt gaactgtcaa tgacaaataa aaattctttt 300
tgattatttt ttgttttcat ttaccagaat aaaaactaag aattaaaagt ttgattacag 360
tc
                                                                   362
<210> 443
<211> 624
<212> DNA
<213> Homo sapiens
```

```
<220>
<221> misc feature
<222> (1)...(624)
<223> n = A, T, C or G
<400> 443
tttttttttt gcaacacaat atacatcaca gtgaaatgtg taatccttgc aaattgcaag 60
ttgaaagaat taaattcaga ggaggggaga gaaagagtac tcagtaggga ctgagcacta 120
aatgottatt ttaaaagaaa tgtaaagago agaaagcaat tcaggotaco ctgoottttg 180
tgctggctag tactccggtc ggtgtcagca gcacgtggca ttgaacattg caatgtggag 240
cccaaaccac agaaaatggg gtgaaattgg ccaactttct attaacttgg cttcctgttt 300
tataaaatat tgtgaataat atcacctact tcaaagggca gttatgaggc ttaaatgaac 360
taacqcctac aaaacactta aacataqata acataqqtqc aaqtactatq tatctqqtac 420
atggtaaaca toottattat taaagtoaac gotaaaatga atgtgtgtgc atatgctaat 480
agtacagaga gagggcactt aaaccaacta agggcctgga gggaaggttt cctggaaaga 540
ngatgettgt getgggteea aatettggte taetatgaee ttggeeaaat tatttaaaet 600
ttgtccctat ctgctaaaca gatc
<210> 444
<211> 425
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (425)
<223> n = A, T, C or G
gcacatcatt nntcttqcat tctttqaqaa taaqaaqatc agtaaatagt tcagaagtgg 60
gaagetttgt eeaggeetgt gtgtgaacee aatgttttge ttagaaatag aacaagtaag 120
ttcattgcta tagcataaca caaaatttgc ataagtggtg gtcagcaaat ccttgaatgc 180
tgcttaatgt gagaggttgg taaaatcctt tgtgcaacac tctaactccc tgaatgtttt 240
gctgtgctgg gacctgtgca tgccagacaa ggccaagctg gctgaaagag caaccagcca 300
cctctgcaat ctgccacctc ctgctggcag gatttgtttt tgcatcctgt gaagagccaa 360
ggaggcacca gggcataagt gagtagactt atggtcgacg cggccgcgaa tttagtagta 420
gtaga
<210> 445
<211> 414
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (414)
<223> n = A, T, C or G
<400> 445
catgtttatg nttttggatt actttgggca cctagtgttt ctaaatcgtc tatcattctt 60
ttctgttttt caaaagcaga gatggccaga gtctcaacaa actgtatctt caagtctttg 120
tgaaattctt tgcatgtggc agattattgg atgtagtttc ctttaactag catataaatc 180
tggtgtgttt cagataaatg aacagcaaaa tgtggtggaa ttaccatttg gaacattgtg 240
aatgaaaaat tgtgtctcta gattatgtaa caaataacta tttcctaacc attgatcttt 300
ggatttttat aatoctacto acaaatgact aggottotoc tottgtattt tgaagcagtg 360
tgggtgctgg attgataaaa aaaaaaaaag tcgacgcggc cgcgaattta gtag
<210> 446
<211> 631
<212> DNA
<213> Homo sapiens
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<220>
<221> misc_feature
<222> (1)...(631)
<223> n = A, T, C or G
<400> 446
acaaattaga anaaagtgcc agagaacacc acataccttg tccggaacat tacaatggct 60
tetgcatgca tgggaagtgt gagcatteta tcaatatgca ggagccatet tgcaggtgtg 120
atgctggtta tactggacaa cactgtgaaa aaaaggacta cagtgttcta tacgttgttc 180
ccggtcctgt acgattcag tatgtcttaa tcgcagctgt gattggaaca attcagattg 240
ctgtcatctg tgtggtggtc ctctgcatca caagggccaa actttaggta atagcattgg 300
actgagattt gtaaactttc caaccttcca ggaaatgccc cagaagcaac agaattcaca 360
gacagaagca aaatacaggg cactacagtt cagacaatac aacaagagcg tccacgaggt 420
taatctaaag ggagcatgtt tcacagtggc tggactaccg agagcttgga ctacacaata 480
cagtattata gacaaaagaa taagacaaga gatctacaca tqttqccttq catttqtqqt 540
aatctacacc aatgaaaaca tgtactacag ctatatttga ttatgtatgg atatatttga 600
aatagtatac attgtcttga tgttttttct g
<210> 447
<211> 585
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (585)
<223> n = A, T, C or G
<400> 447
ccttgggaaa antntcacaa tataaagggt cgtagacttt actccaaatt ccaaaaaggt 60
cctggccatg taatcctgaa agttttccca aggtagctat aaaatcctta taaqqqtqca 120
gcctcttctg gaattcctct gatttcaaag tctcactctc aagttcttga aaacgagggc 180
agtteetgaa aggeaggtat ageaactgat etteagaaag aggaactgtg tgeaceggga 240
tgggctgcca gagtaggata ggattccaga tgctgacacc ttctggggga aacagggctg 300
ccaggtttgt catagcactc atcaaagtcc ggtcaacgtc tgtgcttcga atataaacct 360
gttcatgttt ataggactca ttcaagaatt ttctatatct ctttcttata tactctccaa 420
gttcataatg ctgctccatg cccagctggg tgagttggcc aaatccttgt ggccatgagg 480
attectttat ggggteagtg ggaaaggtgt caatgggact teggteteca tgeegaaaca 540
ccaaagtcac aaacttcaac tccttggcta gtacacttcg gtcta
<210> 448
<211> 93
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (93)
<223> n = A, T, C or G
<400> 448
tgctcgtggg tcattctgan nnccgaactg accntgccag ccctgccgan gggccnccat 60
ggctccctag tgccctggag aggangggc tag
<210> 449
<211> 706
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
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143

```
<222> (1)...(706)
<223> n = A, T, C \text{ or } G
<400> 449
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ttctgancac cgaactgacc atgccaqccc tgccgatggt cctccatggc tccctagtgc 120
cctggagagg aggtgtctag tcagagagta gtcctggaag gtggcctctg ngaggagcca 180
cggggacagc atcctgcaga tggtcgggcg cgtcccattc gccattcagg ctgcgcaact 240
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qtqctqcaaq qcqattaaqt tqqqtaacgc cagggttttc ccagtcncga cgttgtaaaa 360
cgacggccag tgaattgaat ttaggtgacn ctatagaaga gctatgacgt cgcatgcacg 420
cgtacgtaag cttggatect ctagagegge egectactae tactaaatte geggeegegt 480
cgacgtggga tccncactga gagagtggag agtgacatgt gctggacnct gtccatgaag 540
cactgagcag aagetggagg cacaacgene cagacactca cagetactca ggaggetgag 600
aacaggttga acctgggagg tggaggttgc aatgagctga gatcaggccn ctgcncccca 660
gcatggatga cagagtgaaa ctccatctta aaaaaaaaa aaaaaa
<210> 450
<211> 493
<212> DNA
<213> Homo sapiens
<400> 450
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acagttttaa aaggtaaaac aacataaaaa gaaatateet atagtggaaa taagagagte 120
aaatgaggct gagaacttta caaagggatc ttacagacat gtcgccaata tcactgcatg 180
agcctaagta taagaacaac ctttggggag aaaccatcat ttgacagtga ggtacaattc 240
caagtcaggt agtgaaatgg gtggaattaa actcaaatta atcctgccag ctgaaacgca 300
agagacactq tcagagagtt aaaaagtgag ttctatccat gaggtgattc cacagtcttc 360
tcaagtcaac acatctgtga actcacagac caagttctta aaccactgtt caaactctgc 420
tacacatcag aatcacctgg agagctttac aaactcccat tgccgagggt cgacgcggcc 480
                                                                   493
gcgaatttag tag
<210> 451
<211> 501
<212> DNA
<213> Homo sapiens
<220>
<221> misc_feature
<222> (1)...(501)
<223> n = A,T,C or G
<400> 451
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ctcttcqcta ttacqccaqc tqqcqaaaqq qqqatqtqct qcaaqqcqat taaqttgggt 120
aacgccaggg ttttcccagt cncgacgttg taaaacgacg gccagtgaat tgaatttagg 180
tgacnctata gaagagctat gacgtcgcat gcacgcgtac gtaagcttgg atcctctaga 240
geggeegeet actactacta aattegegge egegtegaeg tgggateene aetgagagag 300
tggagagtga catgtgctgg acnotytoca tgaagcactg agcagaagct ggaggcacaa 360
cgcnccagac actcacagct actcaggagg ctgagaacag gttgaacctg ggaggtggag 420
gttgcaatga gctgagatca ggccnctgcn ccccagcatg gatgacagag tgaaactcca 480
tcttaaaaaa aaaaaaaaa a
<210> 452
<211> 51
<212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1)...(51)
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```
<223> n = A, T, C or G
 <400> 452
agacggtttc accnttacaa cnccttttag gatgggnntt ggggagcaag c
                                                                   51
<210> 453
<211> 317
 <212> DNA
<213> Homo sapiens
<220>
<221> misc feature
<222> (1) ... (317)
<223> n = A, T, C or G
<400> 453
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acatetgaag agetagteta teageatetg geaagtgaat tggatggtte teagaaceat 120
ttcacccana cagcctgttt ctatcctgtt taataaatta gtttgggttc tctacatgca 180
taacaaaccc tgctccaatc tgtcacataa aagtctgtga cttgaagttt antcagcacc 240
cccaccaaac tttattttc tatgtgtttt ttgcaacata tgagtgtttt gaaaataagg 300
tacccatgtc tttatta
<210> 454
<211> 231
<212> DNA
<213> Homo sapiens
<400> 454
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taagccacgc cacgctcttg aaggagtctt gaattctcct ctgctcactc agtagaacca 120
agaagaccaa attettetge atcccagett gcaaacaaaa ttgttettet aggtetecae 180
cetteettt teagtgttee aaageteete acaattteat gaacaacage t
<210> 455
<211> 231
<212> DNA
<213> Homo sapiens
<400> 455
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cattgttccg aatgggcttt ccacaggcta cacacaaaa acaggaaaca tgccaagttt 120
gtttcaacgc attgatgact tctccaagga tcttcctttg gcatcgacca cattcagggg 180
caaagaattt ctcatagcac agctcacaat acagggctcc tttctcctct a
<210> 456
<211> 231
<212> DNA
<213> Homo sapiens
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ttccattcag tattatcgtt attattcttg gagaaaccct gtctgtttac tgtaaccttt 120
tgcactcaaa ttcctttatc aggaataact acatagccac tatttacaaa gccattggaa 180
cctttttatt tggtgcagct gctagtcagt ccctgactga cattgccaag t
<210> 457
<211> 231
<212> DNA
<213> Homo sapiens
<220>
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<221> misc_feature
 <222> (1)...(231)
 <223> n = A, T, C or G
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 tatttgattt tattagcaat ctctttcaga agacccttga gatcattaag ctttgtatcc 180
 agttgtctaa atcgatgcct catttcctct gaggtgtcgc tggcttttgt g
 <210> 458
 <211> 231
 <212> DNA
 <213> Homo sapiens
 <400> 458
 aggicitggit coccccacti coactcccct ctactctctc taggacitggg ctgggccaag 60
 agaagagggg tggttaggga agccgttgag acctgaagcc ccaccctcta ccttccttca 120
acaccetaac cttgggtaac agcatttgga attatcattt gggatgagta gaatttccaa 180
ggtcctgggt taggcatttt ggggggccag accccaggag aagaagattc t
<210> 459
<211> 231
<212> DNA
<213> Homo sapiens
<400> 459
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cettegegaa acetgtggtg geceaceagt eetaaeggga eaggaeagag agaeagagea 120
gecetgeact gtttteecte caccacagee atcetgteec teattggete tgtgetttee 180
actatacaca gtcaccgtcc caatgagaaa caagaaggag caccctccac a
                                                                    231
<210> 460
<211> 231
<212> DNA
<213> Homo sapiens
<400> 460
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cctatcaccc tattcttggg ggctgcttct tcacagtgat catgaagcct agcagcaaat 120
cccacctccc cacacgcaca cggccagcct ggagcccaca gaagggtcct cctgcagcca 180
gtggagcttg gtccagcctc cagtccaccc ctaccaggct taaggataga a
<210> 461
<211> 231
<212> DNA
<213> Homo sapiens
<400> 461
cgaggtttga gaagctctaa tgtgcagggg agccgagaag caggcggcct agggagggtc 60
gcgtgtgctc cagaagagtg tgtgcatgcc agaggggaaa caggcgcctg tgtgtcctgg 120
gtggggttca gtgaggagtg ggaaattggt tcagcagaac caagccgttg ggtgaataag 180
agggggattc catggcactg atagagccct atagtttcag agctgggaat t
<210> 462
<211> 231
<212> DNA
<213> Homo sapiens
<400> 462
aggtaccete attgtageea tgggaaaatt gatgtteagt ggggateagt gaattaaatg 60
gggtcatgca agtataaaaa ttaaaaaaaa aagacttcat gcccaatctc atatgatgtg 120
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gaagaactgt tctagaggag	tagagagacc gtatttaatt	aacagggtag tcttctcact	tgggttagag catccagtgt	atttccagag tgtatttagg	tcttacattt a	180 231
<210> 463 <211> 231 <212> DNA <213> Homo	sapiens					
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<210> 464 <211> 231 <212> DNA <213> Homo	sapiens					
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<210> 465 <211> 231 <212> DNA <213> Homo	sapiens		,			
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<210> 468 <211> 3112						

<212> DNA

<213> Homo sapiens <400> 468 cattgtgttg ggagaaaaac agaggggaga tttgtgtggc tgcagccgag ggagaccagg 60 aagatetgea tggtgggaag gacetgatga tacagagttt gataggagae aattaaagge 120 tggaaggcac tggatgcctg atgatgaagt ggactttcaa actggggcac tactgaaacg 180 atgggatggc cagagacaca ggagatgagt tggagcaagc tcaataacaa agtggttcaa 240 cgaggacttg gaattgcatg gagctggagc tgaagtttag cccaattgtt tactagttga 300 gtgaatgtgg atgattggat gatcatttct catctctgag cctcaggttc cccatccata 360 aaatgggata cacagtatga totataaagt gggatatagt atgatotact toactgggtt 420 atttgaagga tgaattgaga taatttattt caggtgccta gaacaatgcc cagattagta 480 catttggtgg aactgagaaa tggcataaca ccaaatttaa tatatgtcag atgttactat 540 gattateatt caateteata gttttgteat ggeecaattt ateeteactt gtgeeteaac 600 aaattgaact gttaacaaag gaatctctgg tcctgggtaa tggctgagca ccactgagca 660 tttccattcc agttggcttc ttgggtttgc tagctgcatc actagtcatc ttaaataaat 720 gattaaataa agaacttgag aagaacaggt ttcattaaac ataaaatcaa tgtagacqca 840 aattttctgg atgggcaata cttatgttca caggaaatgc tttaaaatat gcagaagata 900 attaaatggc aatggacaaa gtgaaaaact tagacttttt ttttttttt ggaagtatct 960 ggatgttcct tagtcactta aaggagaact gaaaaatagc agtgagttcc acataatcca 1020 acctgtgaga ttaaggetet ttgtggggaa ggacaaagat etgtaaattt acagttteet 1080 tecaaageea aegtegaatt ttgaaaeata teaaagetet tetteaagae aaataateta 1140 tagtacatct ttcttatggg atgcacttat gaaaaatggt ggctgtcaac atctagtcac 1200 tttagctctc aaaatggttc attttaagag aaagttttag aatctcatat ttattcctgt 1260 ggaaggacag cattgtggct tggactttat aaggtcttta ttcaactaaa taggtgagaa 1320 ataagaaagg ctgctgactt taccatctga ggccacacat ctgctgaaat ggagataatt 1380 aacatcacta gaaacagcaa gatgacaata taatgtctaa gtagtgacat gtttttgcac 1440 atttccagcc cctttaaata tccacacaca caggaagcac aaaaggaagc acagagatcc 1500 ctgggagaaa tgcccggccg ccatcttggg tcatcgatga gcctcgcct gtgcctggtc 1560 ccgcttgtga gggaaggaca ttagaaaatg aattgatgtg ttccttaaag gatgggcagg 1620 aaaacagatc ctgttgtgga tatttatttg aacgggatta cagatttgaa atgaagtcac 1680 aaagtgagca ttaccaatga gaggaaaaca gacgagaaaa tcttgatggc ttcacaagac 1740 atgcaacaaa caaaatggaa tactgtgatg acatgaggca gccaagctgg ggaggagata 1800 accaegggge agagggteag gattetggee etgetgeeta aaetgtgegt teataaccaa 1860 atcatttcat atttctaacc ctcaaaacaa agctgttgta atatctgatc tctacggttc 1920 cttctgggcc caacattctc catatatcca gccacactca tttttaatat ttagttccca 1980 gatetgtact gtgacettte tacactgtag aataacatta etcattttgt teaaagacee 2040 ttcgtgttgc tgcctaatat gtagctgact gtttttccta aggagtgttc tggcccaggg 2100 gatctgtgaa caggctggga agcatctcaa gatctttcca gggttatact tactagcaca 2160 cagcatgatc attacggagt gaattatcta atcaacatca tcctcagtgt ctttgcccat 2220 actgaaattc atttcccact tttgtgccca ttctcaagac ctcaaaatgt cattccatta 2280 atatcacagg attaactttt ttttttaacc tggaagaatt caatgttaca tgcagctatg 2340 ggaatttaat tacatatttt gttttccagt gcaaagatga ctaagtcctt tatccctccc 2400 ctttgtttga ttttttttcc agtataaagt taaaatgctt agccttgtac tgaggctgta 2460 tacagecaca geeteteece atecetecag cettatetgt cateaceate aacceeteee 2520 atgcacctaa acaaaatcta acttgtaatt ccttgaacat gtcaggcata cattattcct 2580 tctgcctgag aagctcttcc ttgtctctta aatctagaat gatgtaaagt tttgaataag 2640 ttgactatct tacttcatgc aaagaaggga cacatatgag attcatcatc acatgagaca 2700 gcaaatacta aaagtgtaat ttgattataa gagtttagat aaatatatga aatgcaagag 2760 ccacagaggg aatgittatg gggcacgitt gtaagccigg gatgigaagc aaaggcaggg 2820 aaccicatag taicttatat aatatactic atticictat cictatcaca atatccaaca 2880 agcttttcac agaattcatg cagtgcaaat ccccaaaggt aacctttatc catttcatgg 2940

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<212> DNA

<213> Homo sapiens

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<213> Homo sapiens
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caaaattcta aagcgcactc accatgaaat ggataaaggt tacctttggg gatttgcact 180
gcatgaatto tgtgaaaago ttgttggata ttgtgataga gatagagaaa tgaagtatat 240
tatataagat actatgaggt tocotgoott tgottcacat cocaggotta caaacgtgcc 300
ccataaacat tecetetgtg getettgeat ticatatatt tatetaaact ettataatea 360
aattacactt ttagtatttg ctgtctcatg tgatgatgaa tctcatatgt gtcccttctt 420
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	y Ph	e Le	u Ph	e Lei	)				Le	,				l Lei	Leu Ala
Lγ			2 u Ly	e Lei 0	u Lei	ı Phe	e Ph€	e Trr 25 u Val	Let	Asp	o Arq	g Se	r Vai 30 y Asj	l Leu	
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Pr Gl 6	s Gl o Il 5 n Gl 5	u Le 3 e As 0	u Ly 5 p Th	e Le 0 s Ph r Ph y Gl	e Value Pro	This Start This	Phe Lev 40 r Asp 5	e Trp 25 u Val 0 p Pro	Level Photo Ile	e Arc e Ly y Me	g His s Gl 6 t Gl	g Se s Gl u Se 0	r Vai 30 y Asj 5 r Se n Hi	l Let 0 p Arc r Tr s Ty	ı Ala g Ser p Pro
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Gli	u Pr	75	a Gli 5	ı Gly	y Let	ı Ser	760	a Pro	Se:	r Le	u Se:	r Pro 765		су:	s Cys
Pro	770	s Ar	g Ala	a Arç	g Leu	775	a Ph∈	e Arç	j Ası	ı Lei	u Gly 780		Leu	ı Leı	ı Pro
Arg 785	J Let	ı His	s Glr	ı Lev	790	Cys	Arg	y Met	: Pro	795		Leu	Arg	Arç	J Leu 800
•				805	)				810	)				815	
			820	t				825	1				830		Arg
		835	)				840					845			Arg
	850					855					860				Phe
865					870					875		Thr			880
				885					890			Gly		895	
			900					905				Ala	910		_
		915					920					Leu 925			
	930					935					940	Arg			
945					950					955		Phe			960
				965					970			Gly		975	_
			980					985				Ala	990		
		995					1000	)				Glu 100	5		
	1010	)				101	5				10	Leu 20			
Phe 1025	Leu	Leu	Ser	Gln	Val 103	Ala O	Pro	Ser	Leu		Met 35	Gly	Ser	Ile	Val 1040

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Gln Leu Ser Gln Ser Val Thr Ala Tyr Met Val Ser Ala Ala Gly Leu 1045 1050 1055

Gly Leu Val Ala Ile Tyr Phe Ala Thr Gln Val Val Phe Asp Lys Ser 1060 1065 1070

Asp Leu Ala Lys Tyr Ser Ala 1075